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Drug Class Review with New Drug Evaluation: Narcolepsy Agents

Date of Review: July 2019
Generic Name: solriamfetol

End Date of Literature Search: 05/16/2019
Brand Name (Manufacturer): Sunosi™ (Jazz Pharmaceuticals, Inc.)
Dossier Received: Yes

Research Questions:

1. What is the evidence for efficacy of solriamfetol for the treatment of excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA) and how does it compare to current therapy?
2. Is solriamfetol safe for the treatment of excessive daytime sleepiness?
3. Are there subpopulations of adults (i.e. age, gender, ethnicity, disease severity, or comorbid conditions) for whom solriamfetol is more effective or associated with more harms?
4. What is the evidence for efficacy or safety of sodium oxybate for the treatment of narcolepsy, and are there subpopulations for which sodium oxybate is more effective or associated with more harms?

Conclusions:

Solriamfetol

- In patients with narcolepsy, solriamfetol was associated with improvement in sleep latency (measured by the maintenance of wakefulness test [MWT]) compared to placebo after 12 weeks of treatment (low quality evidence; mean difference [MD] with 150 mg of 7.65 minutes; 95% CI 3.99 to 11.31).[1]
- There is moderate quality evidence that solriamfetol improves scores on the Epworth sleepiness scale (ESS) over 12 weeks in patients with moderate to severe narcolepsy (with average difference in scores of 2.2 to 4.7 points).[1] The clinical significance of these differences is unclear.
- In patients with OSA, there is low quality evidence that treatment with solriamfetol improves ESS scores an average of 1.9 to 4.5 points and MWT by 4.5 to 10.7 compared to placebo after 12 weeks of treatment.[2]
- There is no data comparing solriamfetol to other treatments for narcolepsy or OSA, and it is unclear if the observed changes in ESS score or MWT correlate to actual changes in functional status, quality of life, occupation, or social life.
- There is insufficient evidence to assess long-term safety or efficacy of solriamfetol. Solriamfetol labeling has warnings for psychiatric adverse events (including anorexia, anxiety/nervousness, insomnia, irritability) which were observed in clinical trials.[3] Patients with an acute or untreated psychiatric conditions were excluded from clinical trials and the effectiveness or safety in these populations is unclear. FDA labeling recommends only using solriamfetol with caution in these patient populations.
- Solriamfetol use was associated with increases in blood pressure and heart rate. During the clinical trial program, 6 patients treated with solriamfetol experienced cardiovascular events compared to no patients in the placebo group.[4] However, differences in major cardiovascular events are small and studies

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were not powered to determine differences in long-term outcomes. 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. Food and Drug Administration (FDA) labeling recommends against use of solriamfetol in patients with uncontrolled blood pressure and suggests routine monitoring during treatment.[3] Given that solriamfetol has predominate renal metabolism and excretion it is not recommended for treatment in patients with end stage renal disease (ESRD).[3]

Sodium Oxybate

- There is low strength evidence that use of sodium oxybate 9 gm daily in patients with narcolepsy and cataplexy improves number of cataplexy attacks (median difference of 12 attacks per week compared to placebo), symptoms of narcolepsy (mean difference from placebo of 4-5 points on the ESS) and sleep latency (MWT of 10 to 11 minutes). There is insufficient evidence for benefit at lower doses.[5]
- In pediatric patients 7 to 16 years of age experiencing more than 14 cataplexy attacks over 2 weeks, the number of patient-reported cataplexy attacks was unchanged in patients with continued use of sodium oxybate (median attacks per week 0.3) compared to patients randomized to placebo withdrawal (median increase of 12.7 attacks per week; low strength evidence).[5]
- FDA labeling for sodium oxybate contains warnings for neuropsychiatric reactions, central nervous system and respiratory depression, and risk of abuse and misuse. Due to risk of abuse and significant safety concerns, it is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.

Recommendations:

- Add solriamfetol to the Other Stimulants preferred drug list (PDL) class as FDA-approved medication prescribed for "Sleep-Wake" disturbances.
- Designate solriamfetol as voluntary non-preferred and sodium oxybate as non-preferred based upon the current review of efficacy and safety data.
- Recommend implementation of a safety edit for solriamfetol (**Appendix 3**). Safety edits restrict use to FDA-approved ages and doses and include assessment of cardiovascular disease and renal impairment.

Background:

Obstructive sleep apnea (OSA) is defined by repeated upper airway obstruction events with complete or partial apnea during sleep.[6] Diagnosis of OSA is typically confirmed by polysomnography with at least 15 confirmed events per hour or more than 5 events per hour associated with symptoms such as daytime sleepiness, loud snoring, or gasping during sleep.[6] OSA can be categorized based on the number of events per hour ranging from mild disease (5-15 events/hour) to severe disease (≥30 events/hour).[6] OSA occurs most commonly in patients who are overweight, male, or elderly and often occurs in conjunction with comorbid conditions such as hypertension, heart failure, atrial fibrillation, coronary artery disease, stroke, and metabolic syndrome. Untreated OSA is a known risk factor for major cardiovascular events, traffic accidents, and increased mortality.[6] First-line non-pharmacological treatments of OSA include weight reduction in patients who are overweight and continuous positive airway pressure (CPAP) in patients with moderate to severe OSA.[6] In patients who are unresponsive to or unable to tolerate CPAP, other oral appliances may be used as second line therapy.[6] Stimulant medications may be used in conjunction with first-line non-pharmacological treatment to improve excessive daytime sleepiness, but should not be used as monotherapy as they do not correct the underlying disease process. Medications currently FDA-indicated for OSA and narcolepsy include modafinil, armodafinil, and solriamfetol.

Narcolepsy is a clinical syndrome of daytime sleepiness with cataplexy, hypnagogic hallucinations, and sleep paralysis. It is one of the most common causes of disabling daytime sleepiness after obstructive sleep apnea and is characterized by at least 3 months of excessive daytime sleepiness (EDS).[7] Narcolepsy can have a substantial impact on a patient's occupation, education, ability to drive, sexual life, and personality.[4-6] Therefore, the general well-being of patients with narcolepsy is significantly influenced with consequent bad health perception, challenging psychosocial impact, and negative life effects.[4-6] The International

Classification of Sleep Disorders (ICSD-3) classifies the disease in two subtypes: narcolepsy type 1 (NT1) and type 2 (NT2).[7] Type 1 is characterized by cataplexy, a sudden loss of muscle function triggered by strong emotions, or a proven undetectable amount of hypocretin-1 in the cerebrospinal fluid.[7] In type 2, there is no cataplexy and no proven hypocretin-1 deficiency.[7] Diagnosis is typically based on polysomnography (PSG) and a multiple sleep latency test (MSLT) of less than or equal to 8 minutes and at least 2 sleep onset REM periods.[7] Estimated prevalence of narcolepsy ranges from between 25 and 50 per 100,000 individuals in the general population and incidence of narcolepsy with cataplexy varies from 0.02% to 0.067% in North America and worldwide.[8-10] Many other conditions produce such sleepiness and can mimic or coexist with a hypersomnia of central origin such as narcolepsy and it is estimated that narcolepsy is over diagnosed by as much as 50%.[8-10] These differential diagnoses may include sleep disordered breathing syndromes, periodic limb movements, insufficient sleep, psychiatric disorders, medications, and circadian rhythm disorders. [8-10] All of the aforementioned need to be considered in the differential diagnosis as possibly causing or contributing to the excessive sleepiness in a patient with a hypersomnia of central origin. [8-10] According to the American Academy of Sleep Medicine, first-line pharmacological options for patients with narcolepsy include modafinil or methylphenidate.[7] Second-line pharmacological options include sodium oxybate, armodafinil, or combination treatment with 2 agents.[7] Unlike other treatments, sodium oxybate is a central nervous system depressant indicated for narcolepsy. In patients with cataplexy, sodium oxybate may be a reasonable treatment choice though it has high potential for abuse and may be associated with serious side effects including psychosis, confusion, and sedation.[7] Other drugs used off-label for cataplexy include tricyclic antidepressants and fluoxetine, but the quality of published clinical evidence varies.[8]

Common outcomes used in clinical trials to evaluate symptom improvement include the maintenance of wakefulness test (MWT), Epworth sleepiness scale (ESS), and scales to assess overall patient improvement and disease severity. MWT, which requires patients to fight against sleepiness in a soporific situation, is designed to evaluate the severity of sleepiness in patients suffering from Obstructive Sleep Apnea (OSA) or hypersomnia of central origin (Narcolepsy Type I and II).[11,12] The MWT evaluates sleep latency (measured objectively in minutes via electroencephalogram) and is often used in conjunction with the MSLT to comprehensively evaluate the patient's ability to fall asleep (MSLT) and their ability to stay awake (MWT) in a quiet, non-stimulating setting. Because it is conducted in a laboratory setting, however, the MWT may not accurately reflect a patients' typical sleep performance.[11,12] For both the MSLT and the MWT, there have been no large, multicenter, prospectively collected data to establish normative values, and data from smaller, more limited studies have been utilized to extrapolating thresholds for diagnostic and clinical significance.[11,12] In patients with narcolepsy, mean sleep latency on the 40-min MWT of less than 8.0 minutes has been considered abnormal, and values of 8 to 40 minutes are of uncertain significance.[11,12] When used to evaluate the response to a stimulant or CPAP treatment, there are no established thresholds for a change in mean sleep latency. Potential differences in MSLT and MWT significance between the patients with pathologic conditions and non-pathologic conditions are not clear and suggest that states of sleepiness and wakefulness are manifested differently within patient populations.[11,12] Despite apparent limitations, the MWT still provides the strongest support of an individual's ability to stay awake, and the AASM (American Academy of Sleep Medicine) has called this standard "an appropriate expectation for individuals requiring the highest level of safety".[11,12]

The ESS measures the propensity of a patient to fall asleep in daily situations. Patients rate 8 theoretical scenarios on a 0 to 3 scale (total scores range from 0 to 24) with higher scores indicating greater daytime sleepiness. An ESS score of greater than or equal to 10 indicates excessive sleepiness which requires further assessment.[13] Because the ESS is designed to assess sleepiness rather than chronic fatigue (a condition which can exist independently from sleepiness), it may not adequately assess fatigue due to chronic conditions such as multiple sclerosis (MS).[13,14] Studies suggest that changes of 20-25% on the ESS (corresponding to approximate differences of 4-6 points for patients with severe symptoms) may represent clinically meaningful differences in patients with narcolepsy, but consistent thresholds to evaluate clinically meaningful differences have not been established.[14] Overall patient improvement and disease severity are often evaluated with the clinical global impression of severity scale (CGI-S) and clinical global impression of change scale (CGI-C). CGI-C is a clinician rated scale with scores range from 1 (very much improved) to 7 (very much worse).[12] Similarly, CGI-S evaluates clinician-rated disease severity on a 1 to 7 scale with greater scores indicating greater disease severity.

Previous reviews evaluating evidence for modafinil and armodafinil have not identified clinically significant comparative differences in efficacy or harms between modafinil and armodafinil. There is insufficient evidence on health outcomes (i.e., wakefulness, executive functioning, adverse reactions) as well as off-label dosage consideration to delineate any changes to preferred or non-preferred status. Currently modafinil and armodafinil are designated as voluntary non-preferred on the Oregon Health Plan (OHA) preferred drug list (PDL) and are subject to safety edits. Evidence for modafinil and armodafinil was last reviewed in 2015, and off-label use of these agents is evaluated in a separate report from the Drug Effectiveness Review Project. Sodium oxybate and solriamfetol have not yet been reviewed by the Pharmacy and Therapeutics (P&T) committee. Sodium oxybate was FDA-approved in 2002, is currently designated as a physical rather than mental health drug, and has very limited utilization in fee-for-service. Solriamfetol was recently FDA-approved in 2019 and will be designated as a mental health carve-out drug.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Drug Review: Sodium Oxybate
Systematic Reviews:
At the time of this review, no high quality systematic reviews evaluating comparative efficacy or safety of sodium oxybate were identified.

Guidelines:
No high quality guidelines including sodium oxybate were identified.

Randomized Controlled Trials:
A total of 48 citations were manually reviewed from the initial literature search. After further review, 44 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 4 trials are summarized in the table below.

Sodium oxybate was FDA approved in 2002 and is indicated for treatment of cataplexy or excessive daytime sleepiness due to narcolepsy in patients at least 7 years of age.[15] Efficacy of sodium oxybate has been evaluated in several major randomized, placebo-controlled trials (**Table 1**). Most studies were of low quality due to unclear randomization, allocation concealment, and risk for attrition bias.[16-20] One study had risk for reporting bias as prespecified secondary endpoints were unclear, data for reported outcomes were not available for all groups (e.g., functional outcome questionnaires), or authors reported significant conflicts of interest with the manufacturer funding the study.[16-18] Another had high risk of performance bias due to unclear blinding methods.[20] Applicability was limited by

significant exclusion criteria and run-in periods to titrate off current therapy and assess baseline characteristics.[16-20] Compared to placebo in patients with narcolepsy and cataplexy, sodium oxybate 9 grams per day demonstrated a reduction in the median number of cataplexy attacks per week (-16 vs. -4 attacks with placebo),[20] improvement in ESS score (5 vs. 0.5 points),[16-18] and improvement of approximately 10 minutes in the median MWT at 4 to 8 weeks.[16-18]

One study assessed treatment in pediatric patients 7 to 16 years of age with narcolepsy with cataplexy.[5] The study assessed outcomes over a 2 week randomized withdrawal period for patients on established therapy with sodium oxybate.[5] The trial was discontinued early based on a pre-planned interim analysis which demonstrated benefit, and only 63 patients entered the randomization phase. After 2 weeks, the number of patient-reported cataplexy attacks was unchanged in patients continued on treatment (median attacks per week 0.3) and increased in patients randomized to placebo (median attacks per week 12.7).[5] Secondary outcomes of CGI-C for severity of cataplexy attacks and ESS also demonstrated consistent benefits versus placebo.[5] Data is limited by significant exclusion criteria which limit applicability, unclear randomization and allocation concealment methods, early trial discontinued, and significant differences in efficacy which may lead to unblinding of treatment groups.

Table 1. Summary of Pivotal Studies Completed for Sodium Oxybate.

Study Design	Comparison	Population	Primary Outcome	Results
Xyrem International Study Group[16-18] DB, PC, MC, RCT N=401 screened N=353 enrolled N=285 randomized N=228 analyzed Randomization preceded by a 14 day lead-in period; 21 day withdrawal from other anti-cataplectic therapy, 5-18 day washout period, and 14-21 day baseline period.	1. Sodium oxybate 4.5 gm per day 2. Sodium oxybate 6 gm per day 3. Sodium oxybate 9 gm per day 4. Placebo Dose was titrated by 1.5 gm weekly Duration: 8 weeks	Patients with narcolepsy with cataplexy with at least 8 cataplexy attacks per week during the baseline period were 42 centers in the United States, Canada, and Europe	Excessive daytime sleepiness as evaluated by ESS and MWT from baseline to 8 weeks	Change in median ESS from baseline to 8 weeks 1. -1.0; difference vs. placebo of 0.5; p=0.093 2. -2.0; difference vs. placebo of 1.5; p<0.001 3. -5.0; difference vs. placebo of 4.5; p<0.001 4. -0.5 Change in median MWT from baseline to 8 weeks 1. 1.75 minutes; difference vs. placebo p=0.110 2. 1.00 minutes; difference vs. placebo p=0.520 3. 10.13 minutes; difference vs. placebo p<0.001 4. 0 minutes
The US Xyrem Multicenter Study Group[20] DB, PC, MC, RCT N=136 Randomization preceded by a 28 day withdrawal period for other anti-cataplectic therapy, 5-28 day washout period, and 14-21 day baseline period.	1. Sodium oxybate 3 gm daily 2. Sodium oxybate 6 gm daily 3. Sodium oxybate 9 gm daily 4. Placebo Duration: 4 weeks	Adults with narcolepsy and at least 3 cataplexy attacks per week (median 21 attacks)	Change from baseline in the weekly cataplexy attacks	Median change in cataplexy attacks per week from baseline to 4 weeks 1. -7.0; difference vs. placebo 3.3; p-value NR 2. -9.9; difference vs. placebo 5.6; p-value NR 3. -16.1; difference vs. placebo 11.8; p<0.0008 4. -4.3

Black, et al.[19] DB, double-dummy, PC, MC, RCT N=278 enrolled N=221 randomized Randomization preceded by a 7-14 day lead-in period and 14 days to evaluate baseline characteristics.	1. Switch to sodium oxybate 2. Continue current modafinil therapy 3. Add sodium oxybate to current modafinil therapy 4. Switch to placebo Duration: 8 weeks	Adults with narcolepsy on current treatment with modafinil (200-600 mg daily) 44 sites in the US, Canada, the Czech Republic, France, Germany, the United Kingdom, Switzerland, and the Netherlands.	20-minute MWT after 8 weeks	Change in mean MWT (minutes) from baseline to 8 weeks 1. 0.58 (SD 5.68); difference vs. placebo 3.3; p<0.001 2. -0.53 (SD 4.36); difference vs. placebo 2.2; p=0.006 3. 2.68 (SD 5.07); difference vs. placebo 5.4; p<0.001 4. -2.72 (SD 4.54) Mean ESS Score at 8 weeks 1. 12; difference vs. placebo of 4; p<0.001 2. 15; difference vs. placebo of 1; p=0.767 3. 11; difference vs. placebo of 5; p<0.001 4. 16
Plazzi, et al.[5] N=106 enrolled N=99 entered dose stabilization phase N=63 randomized (trial discontinued early due to pre-planned interim analysis) DB, PC, MC, withdrawal, RCT Randomization preceded by a 3-10 week titration and 2 week dose stabilization phase day lead-in period and 14 days to evaluate baseline characteristics.	1. Continue sodium oxybate 2. Placebo withdrawal Duration: 2 week randomized withdrawal phase then open-label treatment for 12 months	Chldren 7-16 years of age with narcolepsy with cataplexy with at least 14 attacks over 2 weeks at baseline 30 sites in USA, Finland, France, Italy, and the Netherlands	Change in patient-reported weekly number of cataplexy attacks	Median change in number of cataplexy attacks per week from baseline to 2 weeks 1. 0.3 (IQR -1.0, 2.5) 2. 12.7 (IQR 3.4, 19.8) P<0.001

Abbreviations: DB = double blind; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; IQR = interquartile range; MC = multicenter; MWT = maintenance of wakefulness test; NR = not reported; PC = placebo-controlled; RCT = randomized controlled trial; SD = standard deviation; US = United States

Similar to other medications FDA-indicated for narcolepsy, FDA labeling for sodium oxybate contains warnings for neuropsychiatric reactions including hallucinations, paranoia, psychosis, aggression, agitation, depression, and suicidality.[15] Parasomnias, including sleepwalking, have also been reported in approximately 6% of patients treated with sodium oxybate during clinical trials.[15] Sodium oxybate has box warnings for central nervous system and respiratory depression and risk of abuse and misuse.[15] Illicit use has been associated with adverse reactions such as seizures, respiratory depression, loss of consciousness, coma, and death. Operation of machinery or vehicles is not recommended for at least 6 hours after taking sodium oxybate, and it is contraindicated in combination with sedative hypnotics or alcohol.[15] Similarly, sodium oxybate should be used cautiously in patients with sleep-related breathing disorders or compromised respiratory function as central apneas and clinically relevant desaturation events have been reported with treatment. Due to risk of abuse and significant safety concerns, it is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.[15] Other significant safety concerns include caution in patients with heart failure, renal impairment or hypertension as sodium oxybate contains a significant amount of sodium (550 mg of sodium per 3

gram dose).[15] Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.[15]

In 3 controlled adult clinical trials in patients with narcolepsy, the most common adverse reactions (incidence ≥5% and twice the rate seen with placebo) in sodium oxybate-treated patients were nausea, vomiting, dizziness, somnolence, enuresis, and tremor.[15] Approximately 10% of patients discontinued treatment due to adverse events compared with 3% of patients receiving placebo.[15] Similar adverse events were reported in a trial of pediatric patients 7 years of age and older with narcolepsy, and common adverse reactions included enuresis (18%), nausea (17%), vomiting (16%), headache (16%), weight decreased (12%), decreased appetite (8%), and dizziness (6%).[15]

New Drug Evaluation: Solriamfetol

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

FDA approval for solriamfetol was based on one phase II trial and 4 phase III clinical trials in patients with narcolepsy or OSA. One ongoing, long-term phase 3 clinical trial in patients with OSA or narcolepsy remains unpublished and is only summarized briefly here. Primary endpoints included in phase III studies were the change in the MWT and change in the patient-reported ESS. For all studies, exclusion criteria were broad and significantly limit applicability in patients with comorbid diagnoses, acute conditions, or mild disease. Specific inclusion and exclusion criteria are listed in **Table 3**.

In patients with narcolepsy, over 60% of patients had marked or severe illness with an average baseline ESS score of 17 (score range 0 to 24 with scores ≥ 10 indicating excessive sleepiness) and sleep latency of approximately 7 minutes.[1] In the phase 3 study, the average change from baseline to 12 weeks in MWT was statistically significant for solriamfetol 150 mg compared to placebo (MD of 7.65 minutes; 95% CI 3.99 to 11.31; p<0.0001) but was not statistically significant for 75 mg daily (MD 2.26 minutes; 95% CI -1.04 to 6.28; p=0.1595).[1] Change in ESS at 12 weeks was statistically improved with both solriamfetol doses compared to placebo with mean differences of 2.2 to 3.8 points.[1] Evidence was limited by differential attrition rates between groups (ranging from 7 to 17% for FDA-approved doses).[1] Results from this phase III study were supported by a phase II RCT of 93 narcolepsy patients in the United States randomized to 150-300 mg/day or placebo.[3] At 12 weeks, patients treated with solriamfetol had a larger change from baseline in MWT compared to placebo (12.8 vs. 2.1 minutes; p<0.0001).[3] The proportion of patients with improvement in CGI-C (defined as a score of 1-3) was greater with solriamfetol compared to placebo (86% vs. 38%; p<0.0001).[3]

In patients with OSA, almost 70% of patients were adherent to primary OSA therapy at baseline.[2,21] Included patients had moderate to severe OSA with an average ESS score at baseline of 15.[2,21] Treatment with solriamfetol improved ESS an average of 1.9 to 4.5 points compared to placebo from baseline to 12 weeks for various FDA-approved doses.[2] Change in MWT was also consistently statistically significant with solriamfetol at 12 weeks with improvements ranging from 4.5 to 10.7 minutes compared to placebo.[2] A dose response was observed for all outcomes. Evidence was limited by high risk for attrition and reporting bias and unclear risk for selection bias. Though adequate randomization and allocation concealment methods were used, there were differences in baseline characteristics between groups. An enriched, randomized, withdrawal study of 75 to 300 mg solriamfetol provided supporting evidence in OSA.[21] Evidence from this trial has limited applicability as a significant proportion of patients did not meet initial eligibility criteria or discontinued treatment during the titration and dose stabilization run-in period. However, patients who were randomized to continue solriamfetol had a significant decline in mean sleep latency (11.2 minutes; 95% CI 7.8 to 14.6; p<0.0001) and ESS scores (-4.6; 95% CI -6.4 to -2.8; p<0.0001) compared to discontinuation of solriamfetol over 2 weeks.[21]

Patients who completed phase 3 trials for solriamfetol were eligible to be enrolled in an open label 6 month extension study.[4] After more than 6 months, patients were randomized to continue solriamfetol or switch to open-label placebo over 2 weeks.[4] Because outcomes for this study (ESS, PGI-C and CGI-C) were patient and provider reported, there is significant risk for performance bias with these results. There were 640 patients enrolled in the trial with a mean baseline ESS of 16 and 282 patients were included in the randomized withdrawal period after at least 6 months.[4] The average change in ESS score during the withdrawal period was 5.3 (standard error 0.4) points for placebo and 1.6 (SE 0.4) points with continued solriamfetol use (MD of -3.7; 95% CI -4.8 to -2.7).[4] Results were similar in patients with OSA or narcolepsy. Approximately 28% of patients continuing solriamfetol reported worsening on the CGIC or PGIC compared to 64% of patients randomized to placebo.[4]

There is no data comparing solriamfetol to other pharmacologic treatments for narcolepsy or OSA and it is unclear if the observed changes in ESS score or MWT correlate to actual changes in functional status, quality of life, occupation, or social life.

Clinical Safety:
Solriamfetol has been studied in 930 patients with narcolepsy or OSA, 396 of which received an FDA-recommended dose of solriamfetol and 255 patients who received treatment for more than 6 months.[3,4] The majority of data included participants prescribed solriamfetol for 12 weeks though safety data also included one trial evaluating efficacy and safety up to 6 months. Common adverse events were consistent with other stimulant medications and included headache, nausea, decreased appetite, anxiety, and insomnia.[3] Adverse reactions appeared to be dose-related and typically resolved with dose reduction or treatment discontinuation. Discontinuations due to adverse events occurred in 3% of patients receiving FDA-approved doses compared to less than 1% of patients who received placebo.[3] Adverse events leading to discontinuation included anxiety (n=2), palpitations (n=2), and restlessness (n=2). Though studied at higher doses, the FDA-recommended maximum dose for solriamfetol was set at 150 mg daily because doses above this threshold do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.[4]

Because psychiatric adverse events (including anorexia, anxiety/nervousness, insomnia, irritability) were observed in clinical trials, solriamfetol should be used cautiously in patients with pre-existing psychosis or bipolar disorder with adequate monitoring to assess for possible emergence or exacerbation of psychiatric symptoms.[3] Patients with a history of psychiatric conditions were excluded from clinical trials and the effectiveness or safety in these populations is unclear.

Slight increases in blood pressure and heart rate were observed in clinical trials with solriamfetol compared to placebo. At 12 weeks, there was an increase in the maximal mean systolic blood pressure (2.4-4.9 mmHg), diastolic blood pressure (1.8-4.2 mmHg), and heart rate (2.9-4.9 beats per minute) from baseline in patients prescribed 37.5 to 150 mg of solriamfetol.[3] Comparatively in the placebo group, the maximal mean change in systolic blood pressure, diastolic blood pressure, and heart rate at 12 weeks was 1.7-3.5 mmHg, 1.4-1.8 mmHg, and 1.7-2.3 beats per minute, respectively.[3] Though the average change in systolic and diastolic blood pressure was small in clinical trials, chronic elevations in blood pressure have been shown to increase the risk of major adverse cardiovascular events.[3] Patients with narcolepsy and OSA often also have multiple other cardiovascular risk factors and average body mass index indicates that the majority of enrolled patients were either overweight or obese. In these clinical trials, patients with any acute medical condition were excluded and the number of patients with comorbid diagnoses such as hypertension, diabetes, and hyperlipidemia were not reported. During the clinical trial program, 6 patients treated with solriamfetol experienced cardiovascular events compared to no patients in the placebo group.[4] However, differences in major cardiovascular events are small and studies were not powered to determine differences in long-term outcomes. It is unclear what impact solriamfetol may have in populations with significant comorbid diagnoses or increased risk for cardiovascular adverse events. FDA labeling recommends against use of solriamfetol in patients with uncontrolled blood pressure and suggests routine monitoring during treatment.[3] Caution should be taken when prescribing solriamfetol in patients at higher risk of

cardiovascular events, in patients with known cardiovascular or cerebrovascular disease, or in patients with moderate to severe renal impairment as they may be at higher risk for adverse events.[3]

Solriamfetol is contraindicated in patients also receiving treatment with a monoamine oxidase inhibitor due to increased risk of hypertensive reactions.[3] Solriamfetol also has a risk of abuse and has been designated as a schedule IV substance by the Drug Enforcement Agency.

FDA-required post-marketing studies include evaluation of maternal and fetal outcomes for women exposed to solriamfetol while pregnant or breast feeding. In animal studies, fetal toxicities, maternal toxicities and adverse effects on growth and development when administered at 4 to 7 times the maximum recommended human dose.[3]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptom improvement (sleep, fatigue, wakefulness)
2) Quality of life
3) Functional impairment
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in the maintenance of wakefulness test (MWT)
2) Change in the Epworth Sleepiness Scale (ESS)

Table 2. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Solriamfetol is a dopamine and norepinephrine reuptake inhibitor. It's mechanism of action to improve wakefulness is unclear, but is thought to be related to dopamine and norepinephrine reuptake in the brainstem arousal systems.
Oral Bioavailability	95%
Distribution and Protein Binding	Volume of distribution: 199 liters 13-19% protein bound
Elimination	95% eliminated unchanged in urine. Dose adjustment is recommended in patients with moderate to severe renal impairment.
Half-Life	7.1 hours
Metabolism	NA

Abbreviations: NA = not applicable

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimen /Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Thorpy, et al.[1] TONES 2 Phase 3 RCT, DB, MC, PC	1. Solriamfetol 300 mg once daily 2. Solriamfetol 150 mg once daily 3. Solriamfetol 75 mg once daily 4. Placebo Titration to target dose was achieved by day 4 Duration: 12 weeks	Demographics: - Mean age (SD) 36.2±13.2 - Female 65.3% - White 80.1% - Mean BMI 28.3 kg/m2 - Cataplexy 50.8% - MWT sleep latency (SD): 7.5±5.7 minutes - ESS score (SD) 17.2±3.2 - CGI-S moderate: 26% - CGI-S marked or severe: 61% Key Inclusion Criteria: - Narcolepsy type 1 or 2 - 18-75 years old - Sleep latency <25 minutes - ESS score ≥ 10 - Patient-reported total sleep time ≥ 6 hours - BMI of 18-45 kg/m^2 Key Exclusion Criteria: - Clinically relevant untreated medical, psychiatric or behavioral disorder associated with excessive sleepiness - History or presence of any acutely unstable medical disorder, psychiatric disorder, or surgical history that could affect patient safety - Current use of medications which could affect excessive sleepiness or cataplexy	ITT: 239 randomized; 231 included in mITT population; NR for each group mITT: (patients who received ≥1 dose and had ≥1 post-baseline assessment) 1. 59 2. 55 3. 59 4. 58 Attrition: 1. 16 (27.1%) 2. 4 (7.3%) 3. 10 (16.9%) 4. 6 (10.3%)	Primary Endpoints (change from baseline to week 12): MWT(minutes) 1. 12.3 (SE 1.4) 2. 9.8 (SE 1.3) 3. 4.7 (SE 1.3) 4. 2.1 (SE 1.3) 1 vs. 4: 10.14 (95% CI 6.39 to 13.90); p<0.0001 2 vs. 4: 7.65 (95% CI 3.99 to 11.31); p<0.0001 3 vs. 4: 2.26 95% CI -1.04 to 6.28); p=0.1595 ESS score 1. -6.4 (SE 0.7) 2. -5.4 (SE 0.7) 3. -3.8 (SE 0.7) 4. -1.6 (SE 0.7) 1 vs. 4: -4.7 (95% CI -6.6 to -2.9); p<0.0001 2 vs. 4: -3.8 (95% CI -5.6 to -2.0); p<0.0001) 3 vs. 4: -2.2 (95% CI -4.0 to -0.3); p=0.0211 Secondary Endpoint: Proportion of Patients with Improvement in Patient Global Impression of Change 1. 84.7% 2. 78.2% 3. 67.8% 4. 39.7% 1 vs. 4: MD 45%; p<0.0001 2 vs. 4: MD 38.5%; p<0.0001 3 vs. 4: MD 28.1%; NS	NA NA NA 45%/3 38%/3 NS	Study withdrawal due to AE 1. 5 (8.5%) 2. 3 (5.1%) 3. 1 (1.7%) 4. 1 (1.7%) Serious AE 1. 0 (0%) 2. 1 (1.7%) 3. 0 (0%) 4. 0 (0%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR; use of interactive voice or web response system for randomization and allocation concealment. Patients were stratified based on presence of cataplexy. Average baseline MWT of 6.1 min for placebo and ≥7.5 minutes for solriamfetol. Other baseline characteristics appear balanced. Performance Bias: LOW. Patients and providers blinded with use of identical opaque capsules. Detection Bias: LOW. Patients and providers blinded with use of identical opaque capsules. Attrition Bias: HIGH. Significant attrition in treatment groups ranging from 7-27%. Imputation was performed based on an average of other assessments for MWT and ESS if there were less than 2 or 3 missing values respectively. Sensitivity analyses performed using different imputation approaches found no substantial differences in treatment effect. Reporting Bias: LOW. Study protocol not available but outcomes reported as specified. Other Bias: UNCLEAR; Funding provided by Jazz Pharmaceuticals who was involved in protocol design and assisted with data collection, analysis and interpretation of data. **Applicability**: Patient: Significant exclusion criteria limit applicability in patients with comorbid conditions or those with acute illness. Included patients had primarily moderate to severe illness. Intervention: FDA approved dose of solriamfetol is 75-150mg daily. Comparator: Placebo appropriate to determine efficacy. Comparison to current treatments such as modafinil or armodafinil may help establish place in therapy. Outcomes: Frequent follow-up at 1, 4, 8, and 12 weeks may not reflect current practice. Significant placebo response for patient reported outcomes. Setting: 50 sites in the United States and Canada. 9 sites in Finland, France, Germany, and Italy.

2. Schweitzer, et al.[2] TONES 3 Phase 3 RCT, DB, MC, PC, PG	1. Solriamfetol 300 mg once 2. Solriamfetol 150 mg once 3. Solriamfetol 75 mg once 4. Solriamfetol 37.5 mg once 5. Placebo Titration to target dose was achieved by day 4 Duration: 12 weeks	Demographics: - Mean age: 54 years - Male: 56-64% - White: 73-79% - BMI: 33 kg/m^2 - mean MWT 12-13 min - mean ESS score: 15 - CGI-S moderate: 37-50% - CGI-S marked: 24-37% - CGI-S severe: 11-15% - Adherent to OSA therapy: 68-73% - H/o surgery: - Placebo: 18% - Solriamfetol: 13% Key Inclusion Criteria: - OSA diagnosis - 18-75 years old - ESS score ≥ 10 - Sleep latency <30 min - Usual patient-reported total sleep time ≥ 6 hours - Current use of primary OSA therapy including mandibular advancement device, PAP, or surgical intervention - In patients without current OSA therapy or with a history of surgery, at least one month of prior primary OSA therapy was required Key Exclusion Criteria: - Bedtime later than 1 am - Job requiring shiftwork - Current drug use which could affect excessive sleepiness or cataplexy - Current or past moderate to severe substance use disorder, nicotine dependence affecting sleep, or other clinically	ITT: 1. 119 2. 118 3. 61 4. 59 5. 119 mITT (patients who received ≥1 dose and had ≥1 post-baseline assessment): 1. 115 2. 116 3. 58 4. 56 5. 114 Attrition: 1. 25 (21.0%) 2. 12 (10.2%) 3. 7 (11.5%) 4. 10 (17.0%) 5. 18 (15.1%)	Primary Endpoints (change from baseline to week 12): MWT (minutes) 1. 13.0 2. 11.0 3. 9.1 4. 4.7 5. 0.2 1 vs. 5: 12.8 (95% CI 10 to 15.6); p<0.0001 2 vs. 5: 10.7 (95% CI 8.1 to 13.4); p<0.0001 3 vs. 5: 8.9 (95% CI 5.6 to 12.1); p<0.0001 4 vs. 5: 4.5 (95% CI 1.2 to 7.9); p<0.0086 ESS score 1. -7.9 2. -7.7 3. -5.0 4. -5.1 5. -3.3 1 vs. 5: -4.7 (95% CI -5.9 to -3.4); p<0.0001 2 vs. 5: -4.5 (95% CI -5.7 to -3.2); p<0.0001 3 vs. 5: -1.7 (95% CI -3.2 to -0.2); p=0.0233 4 vs. 5: -1.9 (95% CI -3.4 to -0.3); p=0.0161 Secondary Endpoint: Proportion of Patients with Improvement in PGI-C 1. 88.7% 2. 89.7% 3. 72.4% 4. 55.4% 5. 49.1% 1 vs. 5: 39.6 (95% CI 28.7 to 50.4); p<0.0001 2 vs. 5: 40.5 (95% CI 29.8 to 51.3); p<0.0001 3 vs. 5: 23.3 (95% CI 8.6 to 38.0); p=0.0035	NA NA 40%/3 40%/3 23%/5	Study withdrawal due to AE 1. 16 (13.6%) 2. 5 (4.3%) 3. 2 (3.2%) 4. 3 (5.2%) 5. 4 (3.4%) Serious AE 1. 0 (0%) 2. 1 (0.8%) 3. 0 (0%) 4. 2 (3.3%) 5. 2 (1.7%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR; use of interactive voice or web response system for randomization and allocation concealment. Patients were stratified based on adherence to primary OSA therapy. Differences in baseline characteristics between groups including CGI-S, race, sex, history of surgical intervention, and adherence to primary OSA therapy. Performance Bias: LOW. Patients and providers blinded with use of identical capsules. Detection Bias: LOW. Patients and providers blinded with use of identical capsules. Attrition Bias: HIGH. Significant attrition in treatment groups ranging from 10-21%. It is unclear how missing data was handled. Reporting Bias: HIGH. All secondary endpoints not reported including functional outcomes, productivity, and health related quality of life. Other Bias: UNCLEAR; Funding provided by Jazz Pharmaceuticals who was involved in protocol design. Data collected by investigators and analyses were conducted by a contract research organization under supervision of the study sponsor. Potential conflicts of interest were not reported for study authors. **Applicability**: Patient: The majority of patients enrolled had moderate to severe illness. Patients with comorbid conditions which may contribute to sleep problems were excluded. Similarly, patients with moderate to severe substance use disorder were excluded. Solriamfetol is a schedule IV substance. Intervention: FDA approved dose of solriamfetol is 75-150mg daily. Follow-up with patients was done at 1, 4, 8, and 12 weeks which may not reflect current practice. Comparator: Placebo appropriate to determine efficacy. Comparison to current treatments such as modafinil or armodafinil may help establish place in therapy. Outcomes: Frequent follow-up at 1, 4, 8, and 12 weeks may not reflect current practice. Significant placebo response for patient reported outcomes.

		relevant behavioral, medical, or psychiatric disorder associated with excessive sleepiness		4 vs. 5: 6.2 (95% CI -9.7 to 22.2); p=0.4447	NS			Setting: 59 research sites in the United States, Canada, France, Germany, and the Netherlands between May 19, 2015, and December 23, 2016
3. Strollo, et al.[21] TONES 4 Phase 3 RCT, DB, MC, PC, enriched, withdrawal study	1. Continuation of solriamfetol 75-300 mg 2. Placebo withdrawal from solriamfetol treatment Phase 1: dose titration to 75mg, 150mg, or 300mg every 3 days to maximize efficacy and tolerability Phase 2: stable dose phase Phase 3: DB randomized withdrawal phase Duration: 6 weeks total (2 weeks during randomized phase)	Demographics (DB period): - Mean age: 56 years - Male: 58-66% - White: 72-81% - CGI-S moderate or markedly ill: 65.5% - Primary OSA therapy: 76-79% - ESS Score: 15-16 - MWT: 12-13 minutes - BMI: 33 kg/m2 - FOSQ-10 Score: 14 Key Inclusion Criteria: - OSA diagnosis - Age 18 to 75 years - Current or prior primary OSA therapy including CPAP, oral appliance or surgical intervention - BMI < 45 kg/m^2 - ESS score ≥ 10 - Sleep latency < 30 min - Usual patient-reported total sleep time ≥ 6 hours - Patients with much or very much improvement on the PGI-C scale during the stable dose phase Key Exclusion Criteria: - Diagnoses other than OSA associated with excessive sleepiness - Nighttime or variable shift work - Excessive caffeine use 1 week prior to the study (definition of excessive use not provided) - Nicotine dependence which affects sleep	ITT: Screened: 402 Phase 1: 174 Phase 2: 157 Phase 3: 124 1. 62 2. 62 mITT (excluded 1 patient who withdrew consent and 1 patient who failed to meet randomization criteria): 1. 60 2. 62 Attrition: 1. 2 (3.2%) 2. 0 (0%)	Primary Endpoint: Change during phase 3 in MWT mean sleep latency (SE) 1. -1.0 (1.4) minutes 2. -12.1 (1.3) minutes MD 11.2 (95% CI 7.8 to 14.6); p<0.0001 Change during phase 3 in ESS score 1. 4.5 (0.7) 2. -0.1 (0.7) MD -4.6 (95% CI -6.4 to -2.8); p<0.0001 Secondary Endpoint: Proportion of patients during phase 3 with decline in PGI-C score 1. 20% 2. 50% Difference -30% (95% CI -46 to -14); p<0.001 Proportion of patients during phase 3 with decline in CGI-C score 1. 21.7% 2. 59% Difference -37.3% (95% CI -53.5 to -12.2); p<0.0001 Change from phase 1 to end of phase 2 or 3 in FOSQ-10 score 1. 16.4 (SD 2.9) 2. 17.4 (SD 3.0) MD 1.2 (95% CI 0.2 to 2.1); p<0.05	NA NA 30%/4 37%/3 NA	Study withdrawal due to AE 6 (3.4%) during titration phase Serious AE 0 (0%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Randomization stratified by adherence to primary OSA therapy. Methods of randomization and allocation concealment were not specified. Baseline characteristics differed between groups for randomized phase. More white and female patients were enrolled in continued treatment. Performance Bias: UNCLEAR. Methods of blinding were not specified. Use of patient and provider reported symptom and functional outcomes may increase risk of bias Detection Bias: UNCLEAR. Methods of blinding were not specified. MWT scored by a central reader. Attrition Bias: LOW. Attrition low and similar between groups. Prior to randomization, 29% of enrolled patients discontinued treatment (n=29) or did not meet eligibility criteria for phase 3 (n=21; PCG-C scale of much or very much improved). Reporting Bias: LOW. Protocol unavailable but all outcomes reported as specified. Other Bias: HIGH. Primary author involved in data analysis and writing manuscript had financial conflicts of interest in the form of consultancy fees and honoraria from the manufacturer. All others including employees of the manufacturer were involved in study design, collection, analysis and interpretation of data and writing the article. **Applicability**: Patient: 4 week run-in titration/stabilization period. Only patients who tolerated treatment and were much or very much improved at 4 weeks were eligible for randomization. Significant exclusion criteria limits applicability. Intervention: During the stable dose phase, 14.6% of patients received 75 mg, 31.8% received 150mg and 53.5% of patients received 300 mg. Comparator: Placebo appropriate to determine efficacy.

		- Surgical history that could affect participant - Any acutely unstable medical, behavioral or psychiatric condition - Current drug use which could affect excessive sleepiness or cataplexy						Outcomes: No long-term outcome data available and there was no difference in functional outcome assessments. Setting: Sites in Finland, France, Germany, Sweden and the United States from May 2015 to November 2016

Abbreviations : AE = adverse effect; BMI = body mass index; CGI-C = clinician global impression of change; CGI-S = clinician global impression of severity; CI = confidence interval; DB = double-blinded; DEA = drug enforcement agency; ESS = Epworth sleepiness scale; FOSQ-10 = functional outcomes of sleep questionnaire; H/o = history of; ITT = intention to treat; MD = mean difference; mITT = modified intention to treat; MC = multi-center; MWT = maintenance of wakefulness test; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; PAP = positive airway pressure; PC = placebo-controlled; PG = parallel-group; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; US = United States; YO = years old

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUNOSI™ safely and effectively. See full prescribing information for SUNOSI.

SUNOSI (solriamfetol) tablets, for oral use, CIV
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

SUNOSI is a dopamine and norepinephrine reuptake inhibitor (DNRI) indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA). (1)

Limitations of Use
SUNOSI is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with SUNOSI. SUNOSI is not a substitute for these modalities. (1)

DOSAGE AND ADMINISTRATION

- Administer once daily upon awakening. Avoid administration within 9 hours of planned bedtime because of the potential to interfere with sleep. (2.2)
- Starting dose for patients with narcolepsy: 75 mg once daily. (2.3)
- Starting dose for patients with OSA: 37.5 mg once daily. (2.4)
- Dose may be increased at intervals of at least 3 days. (2.3, 2.4)
- Maximum dose is 150 mg once daily. (2.3, 2.4)
- Renal impairment (2.5, 8.6, 12.3):
  - Moderate impairment: Starting dose is 37.5 mg once daily.
    - May increase to 75 mg once daily after at least 7 days.
  - Severe impairment: Starting dose and maximum dose is 37.5 mg once daily.
  - End stage renal disease (ESRD): Not recommended.

DOSAGE FORMS AND STRENGTHS

Tablets: 75 mg (functionally scored) and 150 mg. (3)

CONTRAINDICATIONS

Concurrent treatment with a monoamine oxidase inhibitor (MAOI) or use of an MAOI within the preceding 14 days. (4)

WARNINGS AND PRECAUTIONS

- *Blood Pressure and Heart Rate Increases*: Measure heart rate and blood pressure prior to initiating and periodically throughout treatment. Control hypertension before and during therapy. Avoid use in patients with unstable cardiovascular disease, serious heart arrhythmias, or other serious heart problems. (5.1)
- *Psychiatric Symptoms*: Use caution in treating patients with a history of psychosis or bipolar disorders. Consider dose reduction or discontinuation of SUNOSI if psychiatric symptoms develop. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5% and greater than placebo): headache, nausea, decreased appetite, insomnia, and anxiety. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals, Inc. at 1-800-520-5568 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Drugs that Increase Blood Pressure and/or Heart Rate and Dopaminergic Drugs: Use caution when co-administering with SUNOSI. (7.2, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2019

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1946 to June Week 3 2019

1	sodium oxybate.mp. or exp Sodium Oxybate/	1792
2	exp Narcolepsy/	3653
3	1 and 2	224
4	limit 3 to (english language and humans)	206
5	limit 4 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	48

Appendix 3: Safety Edit

Solriamfetol Safety Edit

Goal(s):

- Promote safe use of solriamfetol in patients with narcolepsy and obstructive sleep apnea.

Length of Authorization:

6 to 12 months

Requires PA:

- Solriamfetol

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is the diagnosis funded by OHP? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the request for continuation of therapy at the maintenance dose previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Will prescriber consider a preferred alternative?	**Yes:** Inform prescriber of preferred alternatives (e.g., preferred methylphenidate)	**No:** Go to #6
6. Is the patient 18 years of age or older?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness; Recommend preferred alternative methylphenidate. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA- approved for narcolepsy in this age group.
7. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for less than or equal to 150 mg daily?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the request for concurrent use with a monoamine oxidase inhibitor?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is there baseline documentation of fatigue severity using a validated measure (e.g., Epworth score, Brief Fatigue Inventory, or other validated measure)?	**Yes:** Go to #11 Document baseline scale and score	**No:** Pass to RPh. Deny; medical appropriateness
11. Is there documentation of a recent cardiovascular risk assessment (including blood pressure) with physician attestation that benefits of therapy outweigh risks?	**Yes:** Go to #12 Document recent blood pressure within the last 3 months and physician attestation of cardiovascular risk assessment	**No:** Pass to RPh. Deny; medical appropriateness Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.
12. Does the patient have a diagnosis of end stage renal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13
13. Is the request for treatment of narcolepsy?	**Yes:** Approve for up to 6 months	**No:** Go to #14
14. Is the request for treatment of obstructive sleep apnea and has the patient been stable and adherent to primary OSA treatment (such as CPAP or other primary therapy) for at least one month?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for treatment of obstructive sleep apnea?	**Yes:** Go to #2	**No:** Go to #3
2. Is the patient adherent to primary OSA treatment (e.g., CPAP) based on chart notes?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
3. Is there documentation of a recent blood pressure evaluation (within the last 3 months)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is there documentation of clinical benefit and tolerability from baseline? The same clinical measure used to diagnose excessive daytime sleepiness or fatigue is recommended to document clinical benefit.	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 7/19 (SS)
Implementation: 8/19/19