	Modafanil (Provigil®)	Sodium Oxybate (Xyrem®)	Armodafinil (Nuvigil®)	Solriamfetol (Sunosi®)
Approval	December 1998 Cephalon, Inc.	July 2002 Orpahn Medical	June 2007 Cephalon, Inc.	March 2019 Jazz Pharmaceuticals
Schedule	C-IV	C-III Sodium salt of gamma hydroxybutyrate (GHB active ingredient, Schedule I)	C-IV	C-IV
Indication	To improve wakefulness in adults with excessive sleepiness associated with narcolepsy, OSA, or shift work disorder	Treatment of cataplexy or excessive daytime sleepiness in patients with Narcolepsy	To improve wakefulness in adults with excessive sleepiness associated with narcolepsy, OSA, or shift work disorder	To improve wakefulness in adults with excessive daytime sleepiness associated with narcolepsy or OSA (underlying airway obstruction should be treated for at least 1 month prior to & during Solriamfetol therapy
Non-FDA Uses	• ADHD • MDD (antidepressant augmentation) • Depression Unipolar or bipolar (adjunct) • Multiple sclerosis/Depression (adjunct)/Cancer related fatigue • Schizophrenia (adjunct) • Sleep deprivation • Spastic cerebral palsy • Steinert myotonic dystrophy syndrome	•Alcoholism • Alcohol withdrawal syndrome • Breathing-related sleep disorder • Fibromyalgia • General anesthesia • Opioid withdrawal • Sedation	• Bipolar disorder, depressed phase, in combination with conventional medications	-
MOA (unclear)	•Modafinil increases dopamine by blocking dopamine transporters •decreased GABA-mediated neurotransmission through increased turnover of serotonin & enhanced activity of 5-HT2 receptors	Sodium oxybate's (a CNS depressant) effects are thought to be mediated through GABA-B actions at the noradrenergic, dopaminergic, & thalamocortical neurons	Armodafinil, the R-enantiomer of modafinil, binds to the dopamine transporter & inhibits dopamine reuptake	Selective dopamine and norepinephrine reuptake inhibitor
Generic	Yes	Yes	Yes	No
Dose	100-200mg QDay (400 mg off-label)	4.5 to 9 g QHS in 2 equal divided doses (2.5 to 4 hrs apart)	150 to 250mg QDay	37.5 to 150 mg QDay
Dose adjustment --Renal	Inadequate information	-	Inadequate information	Yes
--Hepatic	Yes	Yes	Yes	No
Administration	with or without food	• Prepare both doses before bedtime by diluting with water • Take 1st dose at least 2 hrs after eating while in bed, lie down immediately, & remain in bed • Take 2nd dose 2.5 to 4 hrs later	with or without food	Avoid taking within 9 hours of bedtime (potential to interfere with sleep)
REMS	No	Yes	No	No
Contraindications	-	• Concurrent use of alcohol or sedative hypnotics • Succinic semialdehyde dehydrogenase deficiency	-	Concomitant use with or within 14 days of a monoamine oxidase (MAO) inhibitor
Boxed Warning	-	• Respiratory depression • Abuse/misuse of GHB → CNS AEs (seizure, respiratory depression, ↓ consciousness, coma & death)	-	-
Warnings & Precautions	• Serious life-threatening rash/Stevens-Johnson Syndrome (SJS) • Angioedema /anaphylaxis reactions • DRESS/Multiorgan hypersensitivity • Persistent sleepiness • Psychiatric symptoms • Effects on ability to drive/use machinery • Known Cardiovascular disease	• CNS depression •Caution clts against hazardous activities requiring mental alertness or motor coordination within the first 6 hrs of dosing or after treatment initiation until sure of sodium oxybate's effect • Abuse & Misuse • REMS (Xyrem Success Program) •Respiratory depression/sleep-disordered breathing • Depression/Suicidality	• Serious life threatening dermatologic reactions • DRESS/Multiorgan hypersensitivity • Angioedema/anaphylaxis reactions • Persistent sleepiness • Psychiatric symptoms • Effects on ability to drive/use machinery • Known Cardiovascular disease	• Blood pressure & heart rate increase • Psychiatric symptoms

		• Behavioral/psych events/confusion/anxiety • Parasomnias		
Pharmacokinetics	• Racemic compound (10% S & 90% R-isomer, different kinetics of enantiomers) • T_{max}: 2 to 4 hrs (delayed ~1 hr with food) • Excretion: Urine (80% as metabolites, unchanged drug <10%); feces (1%) • $T_{1/2}$: 7.5 to 15 hours	• T_{max}: 25 minutes to 1.25 hrs • Metabolism: Liver (extensive) • $T_{1/2}$: 20 to 53 minutes	• T_{max}: 5 to 6.5 hrs (2 hrs fasted state) • Metabolism: Predominantly hepatic • Steady state ~7 days • $T_{1/2}$: ~15 hours • Excretion: Urine (based on modafinil 80% as metabolites, <10% unchanged drug)	Metabolism: minimally metabolized $T_{1/2}$: ~7 hours T_{max}: 2 hours (fasting); delayed by 1 hr with high-fat meal Steady state: 3 days Excretion: Urine (95% as unchanged drug)
Common AEs	GI: Nausea Neurologic: Dizziness, Headache, Insomnia Psychiatric: Anxiety, Feeling nervous	Endocrine metabolic: Weight loss GI: Loss in appetite, N/V Neurologic: Dizziness, headache, somnolence, tremor Renal: Nocturnal enuresis, urinary incontinence	Dermatologic: Rash GI: Loss in appetite, diarrhea, nausea, xerostomia Neurologic: Dizziness, headache, insomnia Psychiatric: Anxiety	GI: Loss in appetite, N/V Neurologic: Headache, insomnia Psychiatric: Anxiety
Serious AEs	Cardiovascular: HTN Dermatologic: DRESS, SJS, TEN Immunologic: Hypersensitivity reaction, Multi-organ Psychiatric: Mania	Neurologic: CNS depression, confusion Psychiatric: Anxiety, risk for suicide, depression, sleep walking disorder Respiratory: Obstructive sleep apnea, O_2 saturation below reference range, respiratory depression	Dermatologic: SJS, TEN Immunologic: Drug reaction with eosinophilia and systemic symptoms (DRESS) Psychiatric: Depression, suicidal thoughts Other: Anaphylaxis, angioedema	Cardiovascular: Increased heart rate Psychiatric: Psychiatric symptom
Comments	• Armodafinil & modafinil does not promote the release of catecholamines (primarily dopamine & norepinephrine) unlike stimulants • Less addictive potential compared to stimulants	Sodium oxybate 9 g a day in patients with narcolepsy & cataplexy showed reduction in cataplexy attacks compared to placebo (median difference: 12 attacks a week); improvement in ESS score (mean difference: 4.5 points) & sleep latency (MWT of ~10 minutes)	• Armodafinil & modafinil appear to be similarly effective, but have not been directly compared • Longer half-life, once-a-day dosing	
Pricing	$ 51/ 30DS	$14040 / 30DS	$ 33/ 30DS	$ 660/ 30DS

Role in therapy

Solriamfetol, the first dual-acting dopamine and norepinephrine reuptake inhibitor, was shown to improve the ability to maintain wakefulness over 12-week compared to placebo

- Narcolepsy
  - improvement in sleep latency measured by maintenance of wakefulness test (MWT)
    - mean difference 7.7 minutes (150 mg group)
  - improved Epworth sleepiness scale (ESS) scores in pts with moderate to severe narcolepsy
    - mean difference: 2.2 to 4.7 points
- OSA
  - Improved MWT and ESS scores
    - mean difference (MWT: 4.5 to 10.7 minutes
    - mean difference ESS scores: 1.9 to 4.5 points

- No studies comparing solriamfetol to other treatment options such as modafinil, methylphenidate, or amphetamines
  - appears to have similar effects as modafinil
  - unclear if changes in MWT or ESS scores correlate to changes in functional status, work, social or quality of life
  - unclear clinical significance
- Inadequate evidence to assess long-term efficacy or safety
- Warning for psychiatric symptoms
  - AEs including anxiety, insomnia, & irritability were observed in clinical trials. Pts with an acute or untreated psychiatric condition were excluded
  - effectiveness/safety in patients with psychosis or bipolar disorder was not studied
- Unclear risk of long-term cardiovascular events in patients with comorbid conditions
  - pts with acute uncontrolled medical condition were excluded
  - Solriamfetol use was associated with increase in BP & HR
  - In pooled 12-week placebo-controlled trials in OSA
    - 3 pts treated with solriamfetol experienced palpitations, 3 felt jittery & 2 chest discomfort (n=235) compared to no patients in the placebo group (n=118)
    - However, the solriamfetol group had twice as many pts as the placebo group
  - Solriamfetol use was associated with increase in BP & HR
  - Monitor for dose-dependent increase in BP & HR

Formulary recommendations:

Add Armodafinil to BHRS formulary, with similar PA criteria as Modafinil

- Off-label use in ADHD
  - Patient tried and failed two trials of stimulants or formulary ADHD medications
- Off-label use in Major Depression
  - Patient tried and failed 4 trials of formulary antidepressants

Nonformulary for Sodium Oxybate and Solriamfetol