<table>
<thead>
<tr>
<th>Approval</th>
<th>Modafinil (Provigil®)</th>
<th>Sodium Oxybate (Xyrem®)</th>
<th>Armodafinil (Nuvigil®)</th>
<th>Solriamfetol (Sunosi®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule</td>
<td>C-IV</td>
<td>C-III</td>
<td>C-IV</td>
<td>C-IV</td>
</tr>
<tr>
<td>Precautions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warnings &amp;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boxed Contraindications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REMS</td>
<td>No</td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Contraindications</td>
<td>-</td>
<td></td>
<td>-</td>
<td>Concomitant use with or within 14 days of a monoamine oxidase (MAO) inhibitor</td>
</tr>
<tr>
<td>Boxed Warning</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Warnings &amp;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precautions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Modafinil (Provigil®)**
- **Approval**: December 1998 Cephalon, Inc.
- **Schedule**: C-IV
- **Indication**: To improve wakefulness in adults with excessive sleepiness associated with narcolepsy, OSA, or shift work disorder
- **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
- **MOA (unclear)**: Modafinil increases dopamine by blocking dopamine transporters • decreased GABA-mediated neurotransmission through increased turnover of serotonin & enhanced activity of 5-HT2 receptors
- **Generic**: Yes
- **Dose**: 100-200mg QDay (400 mg off-label)
- **Dose adjustment --Renal**: Adequate information
- **Dose adjustment --Hepatic**: Adequate information
- **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
- **REMS**: No
- **Contraindications**: -
- **Boxed Warning**: -
- **Warnings & Precautions**: Serious life-threatening rash/Stevens-Johnson Syndrome (SJS) • Angioedema /anaphylaxis reactions • DRESS/Multorgan hypersensitivity • Persistent sleepiness • Psychiatric symptoms • Effects on ability to drive/use machinery • Known Cardiovascular disease

**Sodium Oxybate (Xyrem®)**
- **Approval**: July 2002 Orphan Medical
- **Schedule**: C-III
- **Indication**: Treatment of cataplexy or excessive daytime sleepiness in patients with Narcolepsy
- **Non-FDA Uses**: Alcoholism • Alcohol withdrawal syndrome • Breathing-related sleep disorder • Fibromyalgia • General anesthesia • Opioid withdrawal • Sedation
- **MOA**: Sodium oxybate’s (a CNS depressant) effects are thought to be mediated through GABA-B actions at the noradrenergic, dopaminergic, & thalamocortical neurons
- **Generic**: Yes
- **Dose**: 4 to 9 g QHS in 2 equal divided doses (2.5 to 4 hrs apart)
- **Dose adjustment --Renal**: Adequate information
- **Dose adjustment --Hepatic**: Adequate information
- **Administration**: Yes • Take 1st dose at least 2 hrs before bedtime by diluting with water • Take 2nd dose 2.5 to 4 hrs later
- **REMS**: Yes
- **Contraindications**: Concurrent use of alcohol or sedative hypnotics • Succinic semialdehyde dehydrogenase deficiency
- **Boxed Warning**: Respiratory depression • Abuse/misuse of GHB → CNS AEs (seizure, respiratory depression, ↓ consciousness, coma & death)
- **Warnings & Precautions**: CNS depression • Caution ets 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

**Armodafinil (Nuvigil®)**
- **Approval**: June 2007 Cephalon, Inc.
- **Schedule**: C-IV
- **Indication**: To improve wakefulness in adults with excessive sleepiness associated with narcolepsy, OSA, or shift work disorder
- **Non-FDA Uses**: Bipolar disorder, depressed phase, in combination with conventional medications
- **MOA**: Armodafinil, the R-enantiomer of modafinil, binds to the dopamine transporter & inhibits dopamine reuptake
- **Generic**: Yes
- **Dose**: 150 to 250mg QDay
- **Dose adjustment --Renal**: Yes
- **Dose adjustment --Hepatic**: Yes
- **Administration**: Yes • Avoid taking within 9 hours of bedtime (potential to interfere with sleep)
- **REMS**: No
- **Contraindications**: -
- **Boxed Warning**: -
- **Warnings & Precautions**: Serious life threatening dermatologic reactions • DRESS/Multorgan hypersensitivity • Angioedema/anaphylaxis reactions • Persistent sleepiness • Psychiatric symptoms • Effects on ability to drive/use machinery • Known Cardiovascular disease

**Solriamfetol (Sunosi®)**
- **Approval**: March 2019 Jazz Pharmaceuticals
- **Schedule**: C-IV
- **Indication**: 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**: -
- **MOA**: Selective dopamine and norepinephrine reuptake inhibitor
- **Generic**: No
- **Dose**: 37.5 to 150 mg QDay
- **Dose adjustment --Renal**: Inadequate information
- **Dose adjustment --Hepatic**: Inadequate information
- **Administration**: No
- **REMS**: No
- **Contraindications**: -
- **Boxed Warning**: -
- **Warnings & Precautions**: Blood pressure & heart rate increase • Psychiatric symptoms
### Pharmacokinetics

- **Behavioral/psych events/confusion/anxiety**
  - Parosominas
- **Parasomnias**
  - **Racemic compound (10% S & 90% R-isomer, different kinetics of enantiomers)**
  - **T<sub>max</sub>: 2 to 4 hrs (delayed ~1 hr with food)**
  - **Excretion: Urine (80% as metabolites, unchanged drug <10%); feces (1%)**
  - **T<sub>1/2</sub>: 7.5 to 15 hours**

- **Metabolism: Liver (extensive)**
  - **T<sub>1/2</sub>: 20 to 53 minutes**
  - **T<sub>max</sub>: 25 minutes to 1.25 hrs**

- **Excretion: Urine (80% as metabolites, <10% unchanged drug)**
  - **T<sub>1/2</sub>: 7.5 to 15 hours**
  - **T<sub>max</sub>: 5 to 6.5 hrs (2 hrs fasted state)**

- **Steady state: ~7 days**
  - **T<sub>1/2</sub>: ~15 hours**
  - **Excretion: Urine (based on modafinil 80% as metabolites, <10% unchanged drug)**

- **Metabolism: Predominantly hepatic**
  - **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

### Serious AEs

- **Cardiovascular:** HTN
- **Dermatologic:** DRESS, SJS, TEN
- **Immunologic:** Hypersensitivity reaction, Multi-organ
- **Psychiatric:** Mania

- **Neurologic:** Anxiety, risk for suicide, depression, sleep walking disorder
- **Respiratory:** Obstructive sleep apnea, O₂ saturation below reference range, respiratory depression

- **Dermatologic:** Rash
- **GI:** Loss in appetite, diarrhea, nausea, xerostomia
- **Neurologic:** Dizziness, headache, insomnia
- **Psychiatric:** Anxiety

- **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)**

### 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
  o appears to have similar effects as modafinil
  o unclear if changes in MWT or ESS scores correlate to changes in functional status, work, social or quality of life
  o unclear clinical significance
• Inadequate evidence to assess long-term efficacy or safety
• Warning for psychiatric symptoms
  o AEs including anxiety, insomnia, & irritability were observed in clinical trials. Pts with an acute or untreated psychiatric condition were excluded
  o effectiveness/safety in patients with psychosis or bipolar disorder was not studied
• Unclear risk of long-term cardiovascular events in patients with comorbid conditions
  o pts with acute uncontrolled medical condition were excluded
  o Solriamfetol use was associated with increase in BP & HR
  o 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
  o Solriamfetol use was associated with increase in BP & HR
  o 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