Pharmacy Policy Bulletin: J-0007 Provigil (modafinil) and Nuvigil (armodafinil) – Commercial and Healthcare Reform	
Number: J-0007	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** 1. Other Managed Prior Authorization = Yes w/ Prior Authorization **Healthcare Reform:** Not applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0007-038	**Original Date:** 09/01/1999
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Drugs Product(s):	• Provigil (modafinil) • Nuvigil (armodafinil)

FDA-Approved Indication(s):	• To improve wakefulness in adult patients with excessive sleepiness associated with:
	  ○ Narcolepsy
	  ○ Obstructive Sleep Apnea (OSA)
	  ○ Shift-work disorder (SWD)

Background:	• Provigil and Nuvigil are schedule IV-controlled substances that are wakefulness promoting agents for oral administration. The action of these agents is thought to be similar to that of sympathomimetic agents like amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of sympathomimetic amines. The precise mechanism(s) is unknown. • The FDA recommended dosage of Provigil for narcolepsy or OSA is 200 mg once a day in the morning. Doses up to 400 mg/day of Provigil, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg/day dose. The FDA recommended dose for SWD is 200 mg taken 1 hour before a work shift. • 2007 Guidelines from the American Academy of Sleep Medicine (AASM) recommend higher modafinil dosing and a split dosing strategy for narcolepsy. Level 1 studies showed that either a 400 mg dose at 7:00am followed by a 200 mg dose at 12:00pm or a 200 mg dose at 7:00am followed by a 200 mg dose at 12:00pm was superior to either a single dose of 200 mg or 400 mg once daily at 7:00am. • The use of Provigil in the treatment of fatigue associated with multiple sclerosis (MS) has supporting clinical studies which showed improvement in Epworth Sleepiness Scale (ESS) but resulted in no change of Maintenance of Wakefulness Test (MWT). There is less data evaluating the use of Provigil for the treatment of depression or Parkinson's disease. These later studies are limited to mostly uncontrolled trials and several case reports. All of these studies

	are small in sample size and have a short duration, which make the results difficult to extrapolate. • All patients in the clinical trials for Provigil and Nuvigil for OSA were required to have excessive sleepiness as demonstrated by a score ≥ 10 on the ESS, despite treatment with continuous positive airway pressure (CPAP). Evidence that CPAP was effective in reducing episodes of apnea/hypopnea was required along with documentation of CPAP use. Fully compliant CPAP use was defined as use greater than 4 hours per night on 70% of nights. • Apnea-hypopnea index (AHI) indicates the number of apnea or hypopnea events per hour. A score greater than or equal to 15 indicates moderate to severe apnea. Respiratory disturbance index (RDI) includes the total number of apneas, hypopneas, and respiratory effort related arousals (RERAs) during sleep. A score greater than or equal to 15 indicates moderate to severe apnea. Oxygen desaturation index (ODI) indicates the number of times per hour of sleep that the blood oxygen level drops by 4 or more percentage points from baseline. • The AASM 2009 Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults recommend modafinil for the treatment of residual excessive daytime sleepiness in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness. • Oral appliances (OAs) are devices intended to protrude and stabilize the mandible to maintain a patent airway during sleep. The 2015 AASM Clinical Practice Guideline for the Treatment of OSA and Snoring with Oral Appliance Therapy recommends the consideration of OAs for adults with OSA who are intolerant to CPAP therapy or prefer alternate therapy. The guideline states that CPAP should generally still be used first-line as it has been found to be superior to OAs in reducing AHI, arousal index, and oxygen desaturation index and improving oxygen saturation. The guideline recommends that a custom, titratable appliance be used. A custom OA is created using impressions and models of a patient's oral structures. Titratable OAs have a mechanism that allows for varying amounts of mandibular protrusion. A tongue retaining device is not considered to be an OA. • Inspire Upper Airway Stimulation is FDA approved for adult patients with moderate to severe OSA who are unable to use or get consistent benefit from CPAP. In a study assessing the clinical safety and efficacy of Inspire Upper Airway Stimulation, the median AHI score at 12 months was decreased 68%, from 29.3 events per hour to 9.0 events per hour ($p<0.001$) and the ODI score decreased 70% from 25.4 events per hour to 7.4 events per hour ($p<0.001$). Secondary outcomes demonstrated a reduction in effects of sleep apnea and improved quality of life. • Narcolepsy is a neurological disorder characterized by excessive daytime sleepiness (EDS) and abnormal regulation of sleep-wake cycles. EDS is the primary symptom of narcolepsy and is displayed by all patients to some degree. Cataplexy occurs in 70% of patients and is defined as the sudden, often brief (less than 2 minutes) loss of muscle tone with retained consciousness. It is usually triggered by strong emotions. ○ The American Academy of Sleep Medicine (AASM) 2021 guidelines strongly recommend modafinil, Wakix, sodium oxybate, and Sunosi in the treatment of narcolepsy in adults. They conditionally recommend armodafinil, dextroamphetamine, and methylphenidate. • IH is a neurological disorder characterized by a need to sleep that is not fulfilled after a full night of sleep. Patients sleep a normal or longer-than-normal amount of time at night, but they still feel excessively sleepy during the day. Symptoms include long nighttime or daytime sleep, unrefreshing sleep, difficulty awakening from sleep, cognitive dysfunction, and autonomic symptoms.

	○ The AASM 2021 guidelines strongly recommend modafinil in the treatment of idiopathic hypersomnia (IH) in adults. They conditionally recommend clarithromycin, methylphenidate, Wakix, and sodium oxybate. • Shift work disorder (SWD) is also known as shift work sleep disorder (SWSD). It is categorized as a circadian rhythm sleep disorder. The 2007 AASM guidelines state that modafinil is indicated to enhance alertness during the night shift for SWD. • Diagnostic Criteria ○ The multiple sleep latency test (MSLT) is a day-time sleep study where patients are instructed to try to fall asleep as they take scheduled naps with breaks in between. The time it takes to fall asleep is sleep latency; 97% of people take more than 8 minutes to fall asleep. ○ Polysomnography is an overnight sleep study that measures the amount of time spent in different phases of sleep, in addition to the number of apneic and hypopnea episodes. ○ Sleep-onset rapid eye movement periods (SOREMPs) define the number of periods with REM sleep and can be calculated with a polysomnography or MSLT. People with narcolepsy have more frequent and shorter periods of REM sleep. ○ Individuals with narcolepsy may have lower levels of hypocretins, a neurotransmitter involved in the sleep-wake cycle. Patients may undergo a lumbar puncture to quantify the amount of hypocretin-1 in their cerebrospinal fluid; levels under 110 pg/mL are indicative of narcolepsy. ○ The Epworth Sleepiness Scale (ESS) is a subject assessment completed by the patient, generating a rating representative of their level of excessive daytime sleepiness (EDS). ○ The maintenance of wakefulness test (MWT) is very similar to the MSLT, but patients are instructed to stay awake rather than fall asleep. Sleep latency is also generated from the MWT. • Prescriber Considerations: ○ In OSA, Provigil and Nuvigil are indicated to treat excessive sleepiness and not as the treatment for underlying obstruction. ○ In OSA, if CPAP is the treatment of choice, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating and during treatment with Provigil or Nuvigil for excessive sleepiness. ○ A member may have an Inspire Upper Airway Stimulation device if unable to use or get consistent benefit from CPAP.

Approval Criteria

I. Narcolepsy

A. Initial Authorization

When a benefit, coverage of Provigil (modafinil) or Nuvigil (armodafinil) may be approved when all of the following criteria are met **(1. through 7.)**:

1. The member is 18 years of age or older.

2. The member has a diagnosis of narcolepsy (ICD-10: G47.41).

3. The member meets one (1) of the following criteria **(a., b., or c.)**:

a. The prescriber provides a multiple sleep latency test (MSLT) substantiating both of the following **(i. and ii.)**:

i. Mean sleep latency ≤ 8 minutes.

ii. ≥ 2 sleep-onset rapid eye movement periods (SOREMPs).

b. The prescriber provides polysomnography and an MSLT substantiating all of the following **(i., ii., and iii.)**:

i. MSLT demonstrating a mean sleep latency ≤ 8 minutes.
ii. MSLT demonstrating ≥ one (1) SOREMP.
iii. Polysomnography demonstrating ≥ one (1) SOREMP.

c. The member has a documented hypocretin-1 deficiency defined as one (1) of the following **(i. or ii.)**:
i. Cerebrospinal fluid hypocretin-1 < 110 pg/mL.
ii. Cerebrospinal fluid hypocretin-1 < one-third of the normal value based on laboratory reference range.

4. The prescriber provides documentation of baseline data of one (1) of the following criteria **(a. or b.)**:
a. Excessive daytime sleepiness (EDS) via the Epworth Sleepiness Scale (ESS)
b. Excessive daytime sleepiness (EDS) via Maintenance of Wakefulness Test (MWT).
5. The member has experienced therapeutic failure, intolerance, or contraindication to a plan-preferred generic CNS stimulant (for example, dextroamphetamine, methylphenidate).
6. If the request is for brand Provigil, the member has experienced therapeutic failure or intolerance to both of the following **(a. and b.):**
a. plan-preferred generic armodafinil
b. generic modafinil
7. If the request is for brand Nuvigil, the member has experienced therapeutic failure or intolerance to both of the following products **(a. and b.):**
a. generic armodafinil
b. generic modafinil

B. Reauthorization

When a benefit, reauthorization of Provigil (modafinil) or Nuvigil (armodafinil) may be approved when the following criterion is met **(1.)**:

1. The member has experienced a decrease in daytime sleepiness with narcolepsy as documented by improvement on the Epworth Sleepiness Scale (ESS) or Maintenance of Wakefulness Test (MWT) compared to baseline.

II. Fatigue Associated with Multiple Sclerosis

A. Initial Authorization

When a benefit, coverage of Provigil (modafinil) may be approved when all of the following criteria are met **(1. and 2.)**:

1. The member has a diagnosis of multiple sclerosis (ICD-10: G35), with associated fatigue.
2. If the request is for brand Provigil, the member has experienced therapeutic failure or intolerance to generic modafinil.

B. Reauthorization

When a benefit, reauthorization of Provigil (modafinil) may be approved when the following criterion is met **(1.)**:

1. The member's symptoms of fatigue have improved.

III. Idiopathic Hypersomnia (IH)

A. Initial Authorization

When a benefit, coverage of Provigil (modafinil) may be approved when the following criteria are met **(1. through 8.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of IH. (ICD-10: G47.11 or G47.12)
3. The member does not have a diagnosis of cataplexy.
4. The prescriber provides a polysomnography and/or MSLT substantiating < 2 SOREMPs.
5. The prescriber provides one (1) of the following **(a., b., or c.)**:
a. MSLT demonstrating a mean sleep latency ≤ 8 minutes.
b. Polysomnography demonstrating total 24-hour sleep time ≥ 660 minutes (11 hours).

c. Wrist actigraphy demonstrating ≥ 660 minutes (11 hours) of sleep per 24 hours averaged across at ≥ 7 days of monitoring.

6. The prescriber provides documentation of baseline data of one (1) of the following criteria **(a. or b.)**:
- **a.** Excessive daytime sleepiness (EDS) via the Epworth Sleepiness Scale (ESS)
- **b.** Maintenance of Wakefulness Test (MWT)

7. The member has experienced therapeutic failure, contraindication, or intolerance to a plan-preferred generic CNS stimulant (for example, methylphenidate).

8. If the request is for brand Provigil, the member has experienced therapeutic failure or intolerance to generic modafinil.

B. Reauthorization

When a benefit, reauthorization of Provigil (modafinil) may be approved when the following criterion is met **(1.)**:

1. The member has experienced a decrease in daytime sleepiness as proven by improvement on the ESS or MWT compared to baseline.

IV. Obstructive Sleep Apnea/Hypopnea Syndrome

A. Initial Authorization

When a benefit, coverage of Provigil (modafinil) or Nuvigil (armodafinil) may be approved when all of the following criteria are met **(1. through 5.)**:

1. The member is 18 years of age or older.

2. The member has a diagnosis of obstructive sleep apnea/hypopnea syndrome (OSAHS) (ICD-10: G47.33).

3. The member meets one (1) of the following **(a. or b.):**
- **a.** The member is currently receiving and compliant with positive airway pressure (PAP).
- **b.** The member meets both of the following **(i. and ii.):**
  - **i.** The member has experienced therapeutic failure, intolerance, or contraindication to PAP.
  - **ii.** The member is currently using and compliant with a custom, titratable oral appliance.

4. If the request is for brand Provigil, the member has experienced therapeutic failure or intolerance to both of the following **(a. and b.):**
- **a.** plan-preferred generic armodafinil
- **b.** generic modafinil

5. the request is for brand Nuvigil, the member has experienced therapeutic failure or intolerance to both of the following **(a. and b.)**:
- **a.** generic armodafinil
- **b.** generic modafinil

B. Reauthorization

When a benefit, reauthorization of Provigil (modafinil) or Nuvigil (armodafinil) may be approved when all of the following criteria are met **(1. and 2.)**:

1. The member meets one (1) of the following **(a. or b.):**
- **a.** The member is currently receiving and compliant with positive airway pressure (PAP).
- **b.** The member meets both of the following **(i. and ii.):**
  - **i.** The member has experienced therapeutic failure, intolerance, or contraindication to PAP.
  - **ii.** The member is currently using and compliant with a custom, titratable oral appliance.

2. The member's symptoms of fatigue have improved.

V. Shift Work Disorder

A. Initial Authorization

When a benefit, coverage of Provigil (modafinil) or Nuvigil (armodafinil) may be approved when all of the following criteria are met **(1. through 9):**

1. The member is 18 years of age or older.
2. The member has a diagnosis of shift-work disorder (ICD-10: G47.26).
3. The member has excessive sleepiness or insomnia that is temporarily associated with a recurring work schedule that overlaps the usual time for sleep.
4. The member's symptoms are accompanied by a reduction of total sleep time.
5. The member has experienced symptoms for at least 3 months.
6. The member has sleep log or actigraphy monitoring for at least 14 days including both work and free days.
7. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.
8. If the request is for brand Provigil, the member has experienced therapeutic failure or intolerance to both of the following **(a. and b.):**
   - **a.** plan-preferred generic armodafinil
   - **b.** generic modafinil
9. If the request is for brand Nuvigil, the member has experienced therapeutic failure or intolerance to both of the following **(a. and b.)**:
   - **a.** generic armodafinil
   - **b.** generic modafinil

B. Reauthorization

When a benefit, reauthorization of Provigil (modafinil) or Nuvigil (armodafinil) may be approved when the following criterion is met **(1.):**

1. The member's symptoms have improved.

VI. Quantity Level Limits for Provigil

A. Narcolepsy

When a benefit, coverage of additional quantities of Provigil (modafinil) for a diagnosis of narcolepsy may be approved (up to 600 mg) when the following criterion is met **(1.)**:

1. Daytime sleepiness is inadequately controlled on Provigil (modafinil) 200 mg once daily in the morning.

B. IH, MS Fatigue, OSA, and SWD

When a benefit, coverage of additional quantities of Provigil (modafinil) for a diagnosis of MS Fatigue, OSA, or IH may be approved (up to 400 mg) when the following criterion is met **(1.)**:

1. The member is inadequately controlled on Provigil (modafinil) 200 mg daily.

VII. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

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