Armodafinil (Nuvigil®) and modafinil (Provigil®) are considered medically necessary when ALL of the following criteria are met:

- Individual is 18 years of age or older
- For the treatment of any of the following indications:
  - Adjunctive/Augmentation treatment for Depression and ALL of the following:
    - Armodafinil (Nuvigil) or modafinil (Provigil) will be used concomitantly with at least one oral antidepressant (for example, selective serotonin reuptake inhibitors [SSRIs]).
  - Excessive Daytime Sleepiness associated with Myotonic Dystrophy and ALL of the following:
    - The individual has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months
  - Excessive Daytime Sleepiness Associated with Narcolepsy and ALL of the following:
    - The individual has daily periods of irrepressible need to sleep or lapses into sleep during waking hours, occurring for at least three months
    - A mean sleep latency of less than or equal to 8 minutes and two or more sleep-onset rapid eye movement periods (SOREMPs) are found on an Multiple Sleep Latency Test (MSLT) performed according to standard techniques with a preceding nocturnal polysomnography (PSG) to rule out...
other causes of excessive daytime sleepiness. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT

- The hypersomnia and/or MSLT findings are not better explained by other causes such as insufficient sleep, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal

- Idiopathic Hypersomnia documented by ALL of the following:
  - The individual has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months
  - A Multiple Sleep Latency Test (MSLT) performed according to standard techniques demonstrating BOTH of the following:
    - Less than 2 sleep onset rapid eye movement periods (SOREMPs) or no SOREMPs, if the rapid eye movement (REM) latency on the preceding polysomnogram was less than or equal to 15 minutes
    - Average sleep latency of less than or equal to 8 minutes on MSLT
  - Absence of cataplexy
  - The hypersomnia and/or MSLT findings are not better explained by other sleep disorders (for example, insufficient sleep syndrome [if deemed necessary, by lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed], delayed sleep phase disorder, other medical or psychiatric disorders, the effect of medication or substances or their withdrawal)

- Multiple sclerosis related fatigue

- Excessive Daytime Sleepiness associated with Obstructive sleep apnea / hypopnea syndrome (OSAHS) confirmed by sleep study and ALL of the following:
  - The individual has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months
  - Inadequate response to at least 1 month of non-pharmacologic treatment for OSA [for example, continuous positive airway pressure (CPAP)]
  - Armodafinil (Nuvigil) or modafinil (Provigil) will be used in combination with non-pharmacologic treatment for obstructive sleep apnea (OSA)

- Excessive Daytime Sleepiness associated with Parkinson’s disease related excessive daytime somnolence (EDS) and the following:
  - Armodafinil (Nuvigil) or modafinil (Provigil) will be used in combination with standard Parkinson’s therapy (for example, carbidopa-levodopa, pramipexole, ropinirole)

- Excessive Daytime Sleepiness Associated with Shift work sleep disorder (SWSD) documented by ALL of the following:
  - Individual working at least five overnight shifts per month
  - Insomnia and/or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep
  - Sleep log, completed on work and free days, demonstrating a disturbed sleep and wake pattern
  - The sleep and/or wake disturbance cannot be better explained by another cause (for example, concurrent sleep disorder, medical or neurological disorder, mental disorder, medication use, poor sleep hygiene, substance use disorder)

- Prescribed by or in consultation with a neurologist, pulmonologist, psychiatrist or sleep specialist

**Coverage for Nuvigil and Provigil varies across plans. Refer to the customer’s benefit plan document for coverage details.**

**Where coverage requires the use of preferred products, the following criteria apply.**
For Employer Group:

**Nuvigil**

**BOTH of the following**
- Documented intolerance to 1 generic formulation of Nuvigil
- Documented intolerance to 1 generic formulation of modafinil

**Provigil**

**BOTH of the following:**
- Documented intolerance to 1 generic formulation of Provigil
- Documented intolerance to 1 generic formulation of armodafinil

**Initial authorization is up to 12 months.**

**Modafinil (Provigil) and armodafinil (Nuvigil) are considered medically necessary for continued use when BOTH of the following criteria are met:**
- Initial criteria are met
- Evidence of beneficial clinical response as submitted by the provider

**Reauthorization for up to 12 months.**

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

**Modafinil (Provigil) and armodafinil (Nuvigil) are considered experimental, investigational or unproven for ANY other use including the following:**
- Addiction, dependence and/or abstinence (including withdrawal symptoms) associated with substance abuse
- Adjunctive Therapy in the Treatment of Schizophrenia
- Amyotrophic lateral sclerosis (ALS)
- Antipsychotic-induced Parkinsonism
- Attention-deficit hyperactivity disorder (ADHD)
- Bipolar Disorder, including Bipolar Depression
- Cancer-Related Fatigue
- Combination of stimulant medications (for example, amphetamine, dextroamphetamine/amphetamine, methylphenidate, pitolisant, solriamfetol) and armodafinil, or modafinil, for narcolepsy
- Chronic Fatigue Syndrome
- Cognitive impairment associated with cancer
- Excessive Daytime Sleepiness (EDS) Associated with Primary Insomnia
- Enhancement of Performance in Situations of Induced Sleep Deprivation
- Fibromyalgia
- HIV/AIDS
- Huntington’s disease
- Major depressive disorder (MDD)
- Multiple sclerosis-related nocturnal enuresis
- Postpoliomyelitis syndrome-related fatigue
- Post-Stroke Sleep-Wake Disorders or Sleep Disorders
- Spasticity Due to Cerebral Palsy
- Under arousal related to traumatic brain injury
FDA Approved Indications

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>FDA Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nuvigil</strong></td>
<td>Nuvigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnea (OSA), narcolepsy, or shift work disorder (SWD).</td>
</tr>
<tr>
<td><strong>Limitations of Use:</strong></td>
<td>In OSA, Nuvigil is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating Nuvigil for excessive sleepiness.</td>
</tr>
<tr>
<td><strong>Provigil</strong></td>
<td>Provigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), and shift work disorder (SWD).</td>
</tr>
<tr>
<td><strong>Limitations of Use:</strong></td>
<td>In OSA, Provigil is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating and during treatment with Provigil for excessive sleepiness.</td>
</tr>
</tbody>
</table>

Recommended Dosing

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nuvigil</strong></td>
<td><strong>Dosage in Obstructive Sleep Apnea (OSA) and Narcolepsy:</strong> The recommended dosage of Nuvigil for patients with OSA or narcolepsy is 150 mg to 250 mg taken orally once a day as a single dose in the morning. In patients with OSA, doses up to 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that these doses confer additional benefit beyond that of the 150 mg/day dose. <strong>Dosage in Shift Work Disorder (SWD):</strong> The recommended dosage of Nuvigil for patients with SWD is 150 mg taken orally once a day as a single dose approximately 1 hour prior to the start of their work shift.</td>
</tr>
<tr>
<td><strong>Provigil</strong></td>
<td><strong>Dosage in Narcolepsy and Obstructive Sleep Apnea (OSA):</strong> The recommended dosage of Provigil for patients with narcolepsy or OSA is 200 mg taken orally once a day as a single dose in the morning. Doses up to 400 mg/day, 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. <strong>Dosage in Shift Work Disorder (SWD):</strong> The recommended dosage of Provigil for patients with SWD is 200 mg taken orally once a day as a single dose approximately 1 hour prior to the start of their work shift.</td>
</tr>
</tbody>
</table>

General Background

**Disease Overview**
Narcolepsy is a central nervous system disorder, primarily characterized by excessive daytime sleepiness and cataplexy (sudden loss of muscular tone). The pathophysiology of narcolepsy involves intrusion of aspects of REM sleep (e.g., muscle atonia and dreams) into periods of wakefulness. (Billiard, 2011)
Obstructive sleep apnea (OSA) is a treatable form of sleep disordered breathing characterized by repetitive episodes of apnea, hypopnea, or respiratory effort related arousals (RERA) during sleep. Apnea may be obstructive, central, or mixed. Polysomnography is the collective process of monitoring and recording physiologic data during sleep. Patients with OSAHS often experience sleep fragmentation due to breathing fluctuations. The change in sleep often causes daytime sleepiness. Continuous positive airway pressure (CPAP) assists in improving oxygenation and indirectly improves sleep. However, some patients continue to experience daytime sleepiness with CPAP therapy. Amphetamines and modafinil have been studied to improve daytime sleepiness in the patients with OSAHS. (Young, 2004)

Patients diagnosed with OSA receive education regarding the pathophysiology of OSA and the impact of lifestyle modifications, including weight loss, reduced alcohol consumption, especially at bedtime, and lateral sleeping position (vs. supine). While such noninvasive measures are encouraged, particularly in the obese or those with very poor sleep hygiene, OSA does not usually resolve with these measures alone. Potential treatment options for OSA include treatment with positive airway pressure (PAP), the use of oral appliances, and surgical interventions. Treatment decisions are based on condition severity, the presence of comorbidities and complicating factors, and the patient’s tolerance and response to treatment. (Young, 2004)

Pharmacology
Provigil and Nuvigil have wake-promoting actions similar to sympathomimetic agents including amphetamine and methylphenidate, although their pharmacologic profile is not identical to that of the sympathomimetic amines. The specific mechanism(s) through which either drug supports wakefulness is not known. Armodafinil (R-modafinil) has pharmacological properties similar to those of modafinil (a mixture of R- and S-modafinil), to the extent tested in animal and in vitro studies. The R- and S-enantiomers have similar pharmacological actions in animals. (Clinical Pharmacology 2015)

Professional Societies/Organizations
Adjunctive Treatment for Depression
American Psychiatric Association (APA) practice guidelines for the treatment of patients with major depressive disorder (MDD), state modafinil (or methylphenidate) are potential treatments for sedation associated with antidepressant medications. The APA guidelines state that modafinil has shown benefit when combined with SSRIs, related to specific effects on residual symptoms such as fatigue and hypersomnolence. The guidelines go on to note that there are no clear guidelines regarding the length of time modafinil should be coadministered. (Gelenberg, 2010)

Various trials have used scales involving fatigue measurement to determine the effects of modafinil augmentation in patients with MDD or for sedation/sleepiness due to antidepressant therapy or the disease state. Some of the trials, which included retrospective analysis, open-label studies, and double-blind, placebo-controlled trials, revealed that modafinil may have benefits in depressed patients. In an 8-week, placebo-controlled study involving 311 patients with MDD considered partial responders to stabilized SSRI therapy, modafinil 200 mg once daily (QD) as adjunctive therapy improved the clinical condition as assessed by Clinical Global Impression of Improvement (CGI-I) scores compared with placebo (P = 0.02). (Fava, 2005) A 12-week, open-label extension study of 245 patients who had completed an 8-week double-blind study of modafinil found that the agent continued to improve patients’ overall clinical condition and reduced fatigue and excessive sleepiness when given to augment SSRI therapy in patients with depression. Limited data have investigated modafinil as monotherapy for depression. (Price 2005) While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition.

Excessive Daytime Sleepiness (EDS) Due to Myotonic Dystrophy
American Academy of Sleep Medicine (AASM) guidelines state that modafinil may be effective for the treatment of daytime sleepiness due to myotonic dystrophy. (Morgenthaler, 2007)

Results from clinical trials evaluating the effectiveness of modafinil in treating EDS associated with myotonic dystrophy are equivocal. In a randomized, double-blind, placebo-controlled, 14-day, crossover trial modafinil was evaluated in 40 patients with myotonic dystrophy. Somnolence was reduced in patients receiving modafinil as noted by statistically significant improvements compared with placebo on the Epworth Sleepiness Scale (ESS) scores, and the Stanford Sleepiness Scale. (MacDonald, 2002) In a randomized, double-blind, crossover trial in 19 patients with myotonic dystrophy use of modafinil improved the mean wakefulness scores. (Talbot, 2003) In a randomized, double-blind, placebo-controlled, multicenter, 4-week trial in 28 patients with myotonic muscular
dystrophy type 1 (MMD1), modafinil had no significant effects on daytime somnolence. (Orlikowski, 2009) While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition.

Fatigue Associated with Multiple Sclerosis (MS)

American Academy of Sleep Medicine (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origin state that modafinil may be effective for the treatment of daytime sleepiness due to MS. Other agents used in MS fatigue include pemoline, aspirin, antidepressants (e.g., sertraline, bupropion, fluoxetine, venlafaxine), methylphenidate, and dextroamphetamine; however, these agents are limited by side effects (i.e., pemoline) or have a paucity of clinical data. Although the results with modafinil in clinical trials are heterogeneous, expert opinion considers it to be a first-line anti-fatigue drug for MS patients. While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition. (Morgenthaler, 2007)

Results from clinical trials evaluating the effectiveness of modafinil in the treatment of fatigue associated with MS are equivocal. Modafinil was shown to be effective in treating fatigue associated with MS in one open-label (Zifko, 2002) and one randomized, placebo-controlled study. (Rammohan, 2002) In one randomized, placebo-controlled, double-blind, 5-week, parallel-group trial (n = 115) modafinil and placebo both showed similar effectiveness in treating MS fatigue as rated by the Modified Fatigue Impact Scale (baseline score at screening = 63, and decreased to 52.3 for modafinil and 49.2 for placebo on Day 35; P < 0.001 for both groups vs. baseline and P = 0.27 between groups). (Stankoff, 2005) In one randomized, double-blind, placebo-controlled, 8-week study (n = 121) the mean change in fatigue severity score (FSS) was not significantly improved with modafinil vs. placebo. (Moller, 2011) Modafinil is among the most commonly used medications for fatigue associated with MS (MacAllister, 2005) and, according to expert opinion, is currently a first-line drug for MS patients.

Idiopathic Hypersomnia

American Academy of Sleep Medicine (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origin state that modafinil may be effective for the treatment of daytime sleepiness due to idiopathic hypersomnia. As there may be underlying causes/behaviors associated with EDS, a sleep specialist physician has the training to correctly recognize and diagnose this condition. While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition. (Morgenthaler, 2007)

Modafinil was proven effective in treating idiopathic hypersomnia in several open-label trials and one small randomized, double-blind trial.

Narcolepsy

American Academy of Sleep Medicine (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origin list modafinil as an effective for treatment of daytime sleepiness due to narcolepsy (Standard) and Xyrem as effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (Standard). Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are considered effective for the treatment of daytime sleepiness due to narcolepsy (Guideline). At the time this practice parameter was written, published studies involving armodafinil were limited. (Morgenthaler, 2007)

Obstructive sleep apnea / hypopnea syndrome (OSAHS)

American Academy of Sleep Medicine (AASM) recommendations for the medical therapy of obstructive sleep apnea (OSA) state continuous positive airway pressure (CPAP) is the most uniformly effective therapy and is the only intervention for OSA shown to have favorable impacts on both cardiovascular and neurobehavioral morbidities. When the recommendation was published, there were no widely effective pharmacotherapies for individuals with sleep apnea, with the important exceptions of individuals with hypothyroidism or with acromegaly. Treating the underlying medical condition can have pronounced effects on the apnea/hypopnea index. Stimulant therapy leads to a small but statistically significant improvement in objective sleepiness. (Veasey, 2006; Morgenthaler, 2007)

Parkinson’s disease (PD) related excessive daytime somnolence (EDS)

American Academy of Neurology (AAN) practice parameter on the treatment of nonmotor symptoms of PD, states that for patients with PD and EDS, modafinil is effective in improving patients’ perception of wakefulness,
but is ineffective in objectively improving EDS as measured by objective tests. The practice parameter recommendations indicate modafinil should be considered for patients to improve their subjective perception of EDS; however, it should be noted that patients may experience an improvement in sleep perception without an actual improvement in objective sleep measurements. While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition. (Zesiewicz, 2010)

**American Academy of Sleep Medicine (AASM)** guidelines state that modafinil may be effective for the treatment of daytime sleepiness due to PD. (Morgenthaler, 2007)

Double-blind, randomized, controlled trials, an open-label trial, and case reports have studied modafinil in EDS associated with PD; many patients were receiving PD medication (e.g., pramipexole, levodopa-carbidopa, bromocriptine, amantadine, tolcapone, entacapone, ropinirole). In a double-blind, placebo-controlled crossover study in 21 patients with PD and an ESS score ≥ 10, patients received placebo and modafinil (200 mg QD) for 3 weeks, separated by a washout week. ESS scores were decreased by 3.4 points when modafinil was given compared with a 1.0 increase with placebo (P = 0.039). (Adler, 2003) Another double-blind, randomized, crossover trial in 15 patients with PD and an ESS score ≥ 10 showed similar positive benefit with modafinil in ESS scores compared with placebo (P = 0.011). (Happe, 2001) In contrast, a double-blind, placebo-controlled, 4-week, parallel-designed trial failed to show benefit of modafinil (200 to 400 mg/day given twice daily [BID]) over placebo in ESS scores in 40 patients with EDS related to PD (2.7 and 1.5 point decrease, respectively; P = 0.28). (Ondo, 2005)

**Shift work sleep disorder (SWD)**

Armodafinil and modafinil are FDA-indicated for the treatment of EDS associated with SWSD. The primary pivotal trials supporting the use of armodafinil and modafinil in treating SWSD evaluated volunteers who worked a minimum of five night shifts per month. (Nuvigil, 2017 and Provigil, 2015 [prescribing information])

**The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative:**

No recommendations are available for modafinil or armodafinil.

**Other Covered Uses**

AHFS Drug Information 2020 Edition does not support any off-label uses of Provigil (modafinil) or Nuvigil (armodafinil).

**Compendium and Other Published Studies**

Case series, randomized controlled trials, systematic reviews, and/or meta-analysis have investigated Provigil/Nuvigil for numerous conditions/indications, including addiction, dependence and/or abstinence (including withdrawal symptoms) associated with substance abuse (Joos, 2013), adjunctive treatment of schizophrenia (Rosenthal, 2004), chronic fatigue syndrome (Randall, 2005), amyotrophic lateral sclerosis (Rabkin, 2009), antipsychotic-induced Parkinsonism (Lohr, 2013), bipolar disorder, including bipolar depression (Frye, 2007; Post, 2006; Fernandes, 2003; Calabrese 2010), cognitive impairment associated with cancer (Boele, 2013), enhancement of performance in situations of induced sleep deprivation (Gill, 2006; Caldwell, 2000; Bonnet, 2005; Caldwell 2005), excessive daytime sleepiness (EDS) associated with primary insomnia (Perlis, 2004), fatigue associated with cancer (Jean-Pierre, 2010), fibromyalgia (Schaller, 2001; Schwartz, 2007; Pachas, 2003), Huntington’s disease (Blackwell, 2008), HIV/AIDS (Rabkin, 2010), multiple sclerosis-related nocturnal enuresis (Carrieri, 2007), post-stroke sleep-wake disorders or sleep disorders (Bassetti, 2005; Bivard, 2017) spasticity due to cerebral palsy (Hurst, 2002; Hurst, 2004) and under arousal related to traumatic brain injury (Jha, 2008)

Studies in adults, adolescents and children have shown improvement in attention-deficit hyperactivity disorder (ADHD) symptoms, and various studies report the efficacy of modafinil similar to dextroamphetamine. In 2000, a phase III study conducted by Cephalon, Inc. demonstrated no benefit in decreasing ADHD symptoms in adults when modafinil was compared to placebo. Cephalon, Inc. submitted an NDA for pediatric ADHD in 2005, which led to review of safety data by the FDA Advisory Committee. Despite modafinil’s ability to treat ADHD in children and adolescents, safety signals such as a possible incident of Stevens-Johnson syndrome, psychiatric adverse reactions and lab abnormalities resulted in the drug not receiving approval for this indication. Further safety data was requested by the FDA. Cephalon, Inc. is no longer seeking a pediatric ADHD indication. (Biederman, 2006; Goez, 2012; Greenhill, 2006; Swanson, 2006; Clinical Pharmacology 2015)
Results of controlled studies and meta analyses do not indicate improvement in symptoms of postpoliomyelitis syndrome-related fatigue as compared to placebo, therefore, use in this condition is not supported by evidence. (Chan, 2006)

## Coding/Billing Information

**Note:** Modafinil and armodafinil are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

## References


“Cigna Companies” refers to operating subsidiaries of Cigna Corporation. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Cigna Behavioral Health, Inc., Cigna Health Management, Inc., QualCare, Inc., and HMO or service company subsidiaries of Cigna Health Corporation. The Cigna name, logo, and other Cigna marks are owned by Cigna Intellectual Property, Inc. © 2020 Cigna.