Drug and Biologic Coverage Policy

Effective Date ............................................. 7/1/2020
Next Review Date......................................... 7/1/2021
Coverage Policy Number ............................... 1501

Modafinil / Armodafinil for Individual and Family Plans

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

- Age 18 years of age and older
- For the treatment of any of the following indications:
  - Narcolepsy confirmed by polysomnography (PSG) and Multiple Sleep Latency Test (MSLT)
  - Obstructive sleep apnea / hypopnea syndrome (OSAHS) confirmed by sleep study
  - Shift work sleep disorder (SWD)
  - Multiple sclerosis related fatigue
  - Modafinil (Provigil) only: Parkinson’s disease related excessive daytime somnolence (EDS) AND used in combination with standard Parkinson’s therapy (for example, carbidopa-levodopa, pramipexole, ropinirole)
- Additional specific criteria apply for each drug below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Additional Specific Criteria</th>
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<tbody>
<tr>
<td>Nuvigil</td>
<td>• Documented intolerance to 1 generic formulation of Nuvigil AND</td>
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<tr>
<td></td>
<td>• Documented intolerance to 1 generic formulation of modafinil</td>
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<tr>
<td>Provigil</td>
<td>• Documented intolerance to 1 generic formulation of Provigil AND</td>
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Related Coverage Resources

Obstructive Sleep Apnea Treatment Services
• 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

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
- Amyotrophic lateral sclerosis (ALS)
- Antipsychotic-induced Parkinsonism
- Attention-deficit hyperactivity disorder (ADHD)
- Cognitive impairment associated with cancer
- Fatigue associated with cancer
- HIV/AIDS
- Huntington’s disease
- Major depressive disorder (MDD)
- Multiple sclerosis-related nocturnal enuresis
- Myotonic dystrophy
- Postpoliomyelitis syndrome-related fatigue
- Symptomatic or adjunctive treatment of bipolar depression
- Under arousal related to traumatic brain injury

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.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

**FDA Approved Indications**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Approved Indication</th>
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| Provigil   | Provigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), and shift work disorder (SWD).  
Limitations of Use:  
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. |
| Nuvigil    | Nuvigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnea (OSA), narcolepsy, or shift work disorder (SWD).  
Limitations of Use: |
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<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>
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### Recommended Dosing

#### FDA Recommended Dosing

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<tbody>
<tr>
<td><strong>Provigil</strong></td>
<td>Dosage in Narcolepsy and Obstructive Sleep Apnea (OSA): 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.</td>
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<td>Dosage in Shift Work Disorder (SWD): 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>
<tr>
<td><strong>Nuvigil</strong></td>
<td>Dosage in Obstructive Sleep Apnea (OSA) and Narcolepsy: 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.</td>
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<tr>
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<td>Dosage in Shift Work Disorder (SWD): 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>
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#### Drug Availability

<table>
<thead>
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<tr>
<td><strong>Provigil</strong></td>
<td>Provigil is available as 100 mg or 200 mg capsules.</td>
</tr>
<tr>
<td><strong>Nuvigil</strong></td>
<td>Nuvigil is available as 50 mg, 150 mg, 200 mg or 250 mg capsules.</td>
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### 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

European Federation of Neurological Societies (EFNS)
The EFNS recommends diagnosis of narcolepsy by first interviewing the patient and a full night polysomnography, directly followed by a multiple sleep latency test (MSLT). A follow up polysomnography would be warranted only if the patient has worsening symptoms or other symptoms occur, but not for the purposes of evaluating response to treatment. Modafinil is recommended for narcolepsy symptoms of excessive daytime sleepiness and irresistible episodes of sleep, but is not suggested for symptoms of poor sleep. The EFNS does mention, however, that some patients do report modafinil ameliorates poor sleep. (Billiard, 2011)

American Academy of Neurology (AAN)
The American Academy of Neurology state modafinil should be considered for patients to improve their subjective perception of excessive daytime somnolence. The guidelines note that patients who are treated with modafinil may experience an improvement in sleep perception without an actual improvement in objective sleep measurements. (Zesiewicz, 2010)
The etiology of Parkinson’s disease excessive daytime somnolence (EDS) may be the result of disease process, medications, or other sleep disorders. Two studies assessed the therapeutic efficacy of modafinil in the treatment of EDS in patients with Parkinson’s disease EDS. These studies found that modafinil improved EDS on a subjective level using the Epworth Sleepiness Score (ESS), however, there was no objective improvement in EDS as measured by the maintenance of wakefulness test or Multiple Sleep Latency Test. (Adler et al 2003, Hogl, 2002)

American Academy of Sleep Medicine (AASM)
The American Academy of Sleep recommends 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. (AASM, 2009) The AASM suggests several modalities for treating circadian rhythm sleep disorders (CRSD). Suggested methods to treat shift work disorder include non-pharmaceutical approaches such as planning a sleep schedule and light exposure. Pharmaceutical treatments proposed include scheduled melatonin, hypnotics, stimulants and alerting agents such as modafinil. The AASM mentions that modafinil may be an option for daytime sleepiness due to Parkinson’s disease, multiple sclerosis, myotonic dystrophy or idiopathic hypersomnia. However, supporting data in idiopathic hypersomnia are limited to case reports, retrospective series, and one small randomized trial. The organization is silent on the use of armodafinil. (Mayer, 2015 Morgenthaler 2008, Zesiewicz 2010)

American Psychiatric Association (APA)
The APA published clinical practice guidelines in 2010 for the treatment of patients with major depressive disorder. The APA guidelines address many elements associated with treating major depressive disorder including augmentation therapy in patients who do not respond to initial therapy and potential treatments for side effects associated with antidepressant medications. Modafinil is mentioned in both aforementioned areas. The APA provides several recommendations, with varying levels of supporting evidence, for augmenting therapy in
patients who have not responded fully to treatment. Modafinil is identified as a strategy with less evidence for efficacy and is provided a categorical rating equivalent to the lowest level of clinical confidence possible for a recommendation. (Gelenberg, 2010)

**Department of Veterans Affairs (VA) / Department of Defense (DOD)**
The VA/DoD published clinical practice guidelines in 2016 for the treatment of patients with major depressive disorder. The VA/DoD guidelines address many aspects of treating major depressive disorder including the use of augmentation agents. Neither modafinil nor armodafinil are mentioned in the clinical practice guidelines. (VA/DoD, 2016)

**National Comprehensive Cancer Network (NCCN)**
The NCCN published clinical practice guidelines in 2018 for the treatment of cancer related fatigue. The NCCN guidelines address the treatment of cancer related fatigue associated with many stages of cancer treatment including during active treatment, post-treatment, and end of life care. Modafinil is mentioned on several occasions throughout the guidelines however its use is not recommended for the treatment of cancer related fatigue during any stage of cancer treatment. (Berger, 2018)

**The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative:**
No recommendations are available for modafinil or armodafinil.

**Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)**
There are no CMS National Coverage Determinations for modafinil or armodafinil.

**Clinical Efficacy**

**FDA Approved indications**
Modafinil was compared to placebo in 6 published trials of wakefulness in narcolepsy where all patients were required to have objectively documented excessive daytime sleepiness. Therapeutic response to modafinil was superior to placebo, with little difference in adverse effects, in all clinical trials. No significant difference in efficacy was detected between modafinil 200 mg and 400 mg in the majority of clinical trials. Modafinil demonstrated superior efficacy for improving daytime wakefulness in patients with OSAHS compared to placebo in 3 published clinical trials. Patients suffering from SWD showed greater alertness and quality of life with modafinil therapy compared to placebo in 2 abstracts. (Cephalon, 2015)

Armodafinil was studied in one 12 week trial of improving wakefulness in narcolepsy. Patients received either 150 mg or 250 mg of armodafinil or placebo. Both active drug regimens demonstrated a statistically significant enhanced ability to remain awake compared to placebo. The 250 mg dosage regimen produced a greater magnitude of effect. Armodafinil showed a statistically significant improvement in the ability to remain awake, as compared to placebo in 2 trials of patients with OSAHS, who received either 150 mg or 250 mg of armodafinil. No difference in efficacy was detected between the two dosing regimens. Patients experiencing SWD showed a statistically significant prolongation in time to sleep onset compared to placebo in one 12 week trial. Patients with all conditions were reported to have improvement in their overall clinical condition. (Cephalon, 2017)

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

**Experimental, Investigational, Unproven Uses**
Case series, randomized controlled trials, systematic reviews, and/or meta-analysis have investigated Provigil/Nuvigil for numerous conditions/indications, including multiple sclerosis-related nocturnal enuresis (Carrieri, 2007), under arousal related to traumatic brain injury (Jha, 2008), fatigue associated with cancer (Jean-Pierre, 2010), amyotrophic lateral sclerosis (Rabkin, 2009), Huntington’s disease (Blackwell, 2008), HIV/AIDS (Rabkin, 2010), myotonic dystrophy (Orlikowski, 2009), Cognitive impairment associated with cancer (Boele, 2013), addiction, dependence and/or abstinence (including withdrawal symptoms) associated with substance abuse (Joos, 2013), symptomatic or adjunctive treatment of bipolar depression (Frye, 2007), antipsychotic-induced Parkinsonism (Lohr, 2013) and fatigue associated with fibromyalgia (Schwartz, 2010).
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 et al 2006, Goez et al 2012, Greenhill et al 2006, Swanson et al 2006, Clinical Pharmacology 2015)

Fatigue and sleepiness are common symptoms in major depressive disorder (MDD) patients. These symptoms can result in early discontinuation of treatment which may lead to inadequate treatment. Adjunct therapy to antidepressant therapy may be useful and also improve the Hamilton Rating Scale for Depression (HAM-D). This may be particularly important in patients who are non-responders or only partial responders to antidepressant therapy. Randomized controlled trials with modafinil have demonstrated limited short term benefit (for example, 2 weeks) for wakefulness and fatigue in these patients. In a few studies, an improvement in Clinical Global Impression of change (CGI-c) was noted to favor modafinil, however, there was no statistically significant differences noted with modafinil treatment versus placebo for HAM-D scores. In a multi-center randomized controlled trial, no significant differences were found between modafinil and placebo for daytime sleepiness measured by the rate of change in the Epworth Sleepiness Scale (ESS) score from baseline to week 6 in patients with primary MDD initiating SSRI treatment (n = 72). In addition, the mean end point ESS scores were not statistically significantly between placebo and modafinil. In addition, modafinil was not statistically significant compared to placebo for secondary outcome measures of proportion of subjects achieving response for ESS score, Fatigue Severity Scale (FSS) score, Hamilton Depression Rating Scale or Montgomery-Asberg Depression Rating Scale (MADRS) score. These results suggest only a short-term benefit for wakefulness and fatigue in patients with MDD receiving adequate SSRI treatment. (Dunlop et al 2007, DeBattista et al 2003, Fava et al 2005, 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**