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## Provigil®/Nuvigil™ Prior Authorization Criteria

Brand	Generic	Dosage Form
Nuvigil™	armodafinil	tablet
Provigil®	modafinil	tablet

### FDA APPROVED INDICATIONS<sup>1,26</sup>

Provigil® (modafinil) and Nuvigil™ (armodafinil) are indicated to improve wakefulness in [adult, Provigil] patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder.

In OSAHS, Provigil and Nuvigil are indicated as an adjunct to standard treatment(s) 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 Provigil. If Provigil is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

In all cases, careful attention to the diagnosis and treatment of the underlying sleep disorder(s) is of utmost importance. Prescribers should be aware that some patients may have more than one sleep disorder contributing to their excessive sleepiness.

The effectiveness of modafinil and armodafinil in long-term (for Provigil = greater than 9 weeks in narcolepsy clinical trials and 12 weeks in OSAHS and SWSD clinical trials; for Nuvigil = greater than 12 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to prescribe Provigil or Nuvigil for an extended time in patients with narcolepsy, OSAHS, or SWSD should periodically reevaluate long-term usefulness for the individual patient.

### RATIONALE FOR PRIOR AUTHORIZATION

The intent of the Provigil/Nuvigil Prior Authorization (PA) Criteria is to appropriately select patients for therapy according to indications in product labeling and/or clinical guidelines and/or clinical studies and according to dosing recommended in product labeling. Modafinil and armodafinil are indicated to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD).<sup>1,26</sup> Modafinil has been used to treat other indications not approved by the Food and Drug Administration (FDA) including attention deficit/hyperactivity disorder (ADHD),<sup>2-5</sup> as an adjunct to antidepressants,<sup>6-8</sup> and to combat general fatigue unrelated to lack of sleep such as in Parkinson's disease,<sup>9-11</sup> multiple sclerosis,<sup>12-14</sup> and chronic fatigue syndrome.<sup>15</sup> Modafinil has also been studied for the treatment of cocaine addiction<sup>16</sup>, relief of acute pain<sup>17</sup>, myotonic dystrophy<sup>18,19</sup>, post-polio<sup>20</sup>, and schizophrenia.<sup>21,22</sup> There is little evidence to support use of modafinil for these off-label indications. Armodafinil is currently being studied for the treatment of fatigue in cancer, HIV/AIDS, fibromyalgia, and sarcoidosis, as well as use in major depression, traumatic brain injury, and jet lag, and also effects on brain function in schizophrenia.<sup>25</sup> There are currently insufficient data supporting the use of armodafinil for any of these off-label uses.

The PA criteria will approve modafinil or armodafinil when prescribed according to product labeling for patients sixteen years and older. Safety and effectiveness in individuals below sixteen years of age have not been established.<sup>1,26</sup> Serious skin rashes, including erythema multiforme major and Stevens-Johnson Syndrome have been associated with modafinil use in pediatric patients. In controlled and open-label clinical studies of modafinil in pediatric patients, treatment emergent adverse events of the psychiatric and nervous system included Tourette's syndrome, insomnia, hostility, increased cataplexy, increased hallucinations and suicidal ideation. Transient leucopenia, which resolved without medical intervention, was also observed.<sup>1,26</sup>

Approvals will be indefinite for the diagnosis of narcolepsy and twelve months for all other indications. Indefinite approvals may be subject to reevaluation if selection criteria change or safety issues become apparent.

The PA criteria for Provigil and Nuvigil will also limit dispensed quantities to one tablet per day. Prescribing information for modafinil recommends a dose of 200 mg given once a day in the morning for narcolepsy and OSAHS.<sup>1</sup> When prescribed for shift work sleep disorder the dose should be taken approximately one hour prior to the start of the work shift.<sup>1</sup> Single doses of modafinil up to 400 mg per day have been well tolerated, but there is no consistent evidence that this dose is more efficacious than a 200 mg per day dose.<sup>1</sup> For armodafinil, prescribing information recommends single daily doses of 150 mg or 250 mg for OSAHS or narcolepsy. The recommended dose of armodafinil for SWSD is 150 mg given daily approximately 1 hour prior to the start of their work shift.<sup>26</sup>

#### *Off-label use of modafinil*

Methylphenidate and amphetamines have been commonly used for the treatment of ADHD and because these psychostimulants are effective for treatment of narcolepsy, modafinil has been studied as therapy for ADHD. Published studies indicate that modafinil may be efficacious in treating symptoms of ADHD but studies have been small and of short duration.<sup>2-5</sup> It is unknown if beneficial effects are maintained with chronic administration. Studies have not been adequately powered to address safety concerns. There are no head-to-head comparisons between modafinil and psychostimulants to define its role in the treatment of ADHD.

Cephalon, the manufacturer of modafinil, had submitted a supplemental new drug application to market modafinil under the trade name, Sparlon, in doses of 85 mg, 170 mg, 255 mg, 340 mg and 425 mg tablets for the treatment of ADHD in children and adolescents six through seventeen years of age.<sup>23</sup> However, FDA approval was denied after the FDA advisory committee voted 12-to-1 against Sparlon due to concerns about a number of reported cases of skin rash reactions in a patient trial involving 1,000 patients.<sup>23</sup> One skin rash report was thought to be Stevens-Johnson syndrome.<sup>23</sup> Cephalon decided to discontinue development of Sparlon for pediatric use.

The use of adjuvant modafinil for the treatment of residual excessive sleepiness and fatigue in major depressive disorder has been evaluated in two published double-blind, placebo-controlled studies. The first study enrolled 136 patients with partial symptom improvement following treatment with standard antidepressants.<sup>6</sup> Patients were given modafinil or placebo in addition to their previous antidepressant regimen and followed for six weeks.<sup>6</sup> After the second week, modafinil-treated patients demonstrated a greater improvement in fatigue than placebo-treated patients. However, at study end, there was no difference in the resolution of fatigue between groups.<sup>6</sup> Patients treated with modafinil also demonstrated a greater resolution of excess sleepiness compared to placebo after one week but this difference was not significant at week six.<sup>6</sup> No difference was noted between treatment groups in resolution of depressive symptoms overall.<sup>6</sup>

The second study involved a larger sample size (N=311), a longer duration of treatment (8 weeks), and enrolled patients experiencing sleepiness and fatigue.<sup>7</sup> In this study there was a numerical difference between modafinil and placebo in the resolution of depressive symptoms but the difference was not statistically significant.<sup>7</sup> A subgroup analysis of patients with moderate to severe depression found that modafinil was significantly more effective than placebo ( $p \leq 0.05$ ) in resolving depressive

symptoms after 8 weeks. Modafinil-treated patients also demonstrated greater improvement than placebo at endpoint in the Clinical Global Impressions-Improvement scale. A 12-week, open-label extension of this study experienced a dropout rate (24%) making results unreliable.<sup>8</sup> Although modafinil may be effective in resolving depressive symptoms overall in patients who partially respond to antidepressants, its efficacy in treating the depressive symptoms of sleepiness and fatigue has not been established.

Randomized double-blind, placebo-controlled trials evaluating modafinil for the treatment of excessive daytime sleepiness (EDS) in patients with Parkinson's disease have been small and results have been inconclusive.<sup>9-11</sup> In the largest study (N=40), modafinil failed to significantly improve EDS in Parkinson patients compared to placebo.<sup>11</sup>

Results of a phase 2 study (N=72)<sup>12</sup> and an open-label dose-finding study (N=50)<sup>13</sup> evaluating the use of modafinil for treating symptoms of fatigue in multiple sclerosis have indicated efficacy of modafinil in improving symptoms of sleepiness and fatigue in MS. However, another randomized, placebo-controlled, double-blind study assessing the efficacy of modafinil (N=115), concluded that there was no improvement in fatigue in MS patients treated with modafinil versus placebo according to the Modified Fatigue Impact Scale.<sup>14</sup>

There is limited evidence supporting the efficacy of modafinil for the treatment of cocaine dependence,<sup>16</sup> acute pain,<sup>17</sup> chronic fatigue syndrome,<sup>15</sup> myotonic dystrophy,<sup>18,19</sup> post-polio,<sup>20</sup> or schizophrenia.<sup>21,22</sup>

The World Anti-Doping Agency (WADA) added modafinil to the list of prohibited substances in August 2004 after a runner in the 2003 World Track and Field Championships tested positive for the agent.<sup>24</sup> It is unknown how widely modafinil is used for enhancing athletic performance and there no studies are available indicating if there is a positive impact.

There are on-going clinical studies evaluating modafinil for the treatment of fatigue in cancer, HIV/AIDS, PD, ALS, and MS as well as studies for use in cocaine, methamphetamine, and nicotine addiction and use in traumatic brain injury, effects on brain function in schizophrenia, and effects on memory and attention in Lupus patients.<sup>25</sup> There are also on-going clinical trials evaluation armodafinil for the treatment of fatigue in cancer, HIV/ADIS, fibromyalgia, and sarcoidosis, as well as use in major depression, traumatic brain injury, and jet lag, and also effects on brain function in schizophrenia.<sup>25</sup>

## **PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**

### ***Provigil® (modafinil), Nuvigil™ (armodafinil)***

#### **Initial and Renewal Evaluation**

1. Is the patient 16 years of age or older?  
If yes, continue to 2. If no, deny.
2. Is the patient's diagnosis an FDA-approved labeled indication (narcolepsy, obstructive sleep apnea/hypopnea syndrome [OSAHS], shift work sleep disorder)?  
If yes, continue to 3. If no, deny.
3. Can the prescribed dose be accomplished with a quantity of one tablet per day?  
If yes, approve indefinitely for one tablet per day if prescribed for narcolepsy, approve for 12 months for one tablet per day for OSAHS or shift work sleep disorder.  
If no (quantities are greater than one tablet per day), deny.

## **SUMMARY**

The intent of the prior authorization criteria for modafinil and armodafinil are to appropriately select patients for therapy according to labeled indications and recommended dosing. Due to lack of safety and efficacy data in patients under the age of sixteen, modafinil and armodafinil will not be approved

for this age group. Modafinil and armodafinil are indicated to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder. The use of modafinil for attention deficit/hyperactivity disorder has been reviewed but not approved by the Food and Drug Administration. There are insufficient data supporting efficacy for the use of modafinil for improving wakefulness or decreasing fatigue in other diagnoses such as depression, multiple sclerosis, Parkinson Disease, chronic fatigue syndrome or for treatment of cocaine addiction. There are also insufficient data supporting efficacy for use of armodafinil for any off-label uses.

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**Document History**

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