Medication Policy Manual

Topic: Provigil®, modafinil

Date of Origin: April 22, 2002

Committee Approval Date: September 11, 2015

Next Review Date: September 2016

Effective Date: October 1, 2015

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Modafinil (Provigil®) is a medication used to treat excessive sleepiness. Modafinil has wake promoting actions like amphetamines and caffeine, although the exact way modafinil works in the body is unknown.
Policy/Criteria

I. Most contracts require prior authorization approval of modafinil prior to coverage. Modafinil may be considered medically necessary in patients when one of criteria A, B, or C below is met.

A. Excessive sleepiness associated with narcolepsy (diagnosed by the criteria of DSM-IV-TR, Appendix 1) when at least one formulary/preferred treatment, such as methylphenidate or dextroamphetamine, has been ineffective or not tolerated.

OR

B. Excessive daytime sleepiness associated with obstructive sleep apnea/hypopnea syndrome when both criteria 1 and 2 below are met:

1. There is documentation of residual excessive daytime sleepiness associated with obstructive sleep apnea/hypopnea syndrome.

AND

2. There is documentation that the patient has been compliant with CPAP or BiPAP for at least 2 months.

OR

C. Excessive sleepiness associated with shift-work sleep disorder (circadian rhythm sleep disorder) when all criteria 1 through 4 below are met.

1. Diagnosis is made using the criteria from International Classification of Sleep Disorders (ICSD; Appendix 2).

AND

2. Sleep disturbance causes specific measurable functional impairment in social, occupational, or other important areas of functioning that has persisted at least 3 months.

AND

3. Sleep disturbance is not due to otherwise reversible conditions. Other reversible conditions may include, but are not limited to, another sleep disorder, mental disorder, or physiological effects of another substance.

AND

4. Non-pharmacologic therapies have been inadequate in improving functional impairments. Examples of non-pharmacologic therapies include, but are not limited to, planned sleep schedules and timed light exposure.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers modafinil to be a self-administered medication.

B. Quantity Limitations
1. Narcolepsy and obstructive sleep apnea/hypopnea syndrome:
   a. When prior authorization is approved, modafinil may be authorized in quantities of 200 mg per day.
   b. Doses up to 400 mg per day may be considered medically necessary when there is documentation showing that 200mg daily does not provide adequate response.

2. Shift-work sleep disorder: When prior authorization is approved, modafinil may be authorized in quantities of 200 mg per day.

C. Authorization shall be reviewed in the timeframes defined below to confirm that current medical necessity criteria are met and that the medication is effective.

1. Narcolepsy: Authorization shall be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

2. Obstructive Sleep Apnea/Hypopnea:
   a. Initial authorization: Authorization shall be reviewed at 6 months to confirm that the patient continues to be adherent on CPAP while on modafinil.
   b. Continued authorization: After initial approval, authorization shall be reviewed at least annually to confirm that the patient continues to be adherent on CPAP while on modafinil.

3. Shift-work Sleep Disorder: Authorization shall be renewed at least annually confirm that current medical necessity criteria are met and that the medication is effective.

III. Modafinil is considered not medically necessary for the following:
   A. The treatment of attention deficit/hyperactivity disorder (ADHD) (pediatric or adult).
   B. Concomitant use with armodafinil (Nuvigil).

IV. Modafinil is considered investigational when used for all other conditions, including, but not limited to, the following:
   A. Amphetamine and/or alcohol dependence.
   B. Augmentation in patients with major depressive disorder.
   C. Fatigue associated with any other condition not listed above, including, but not limited to, the following:
      a. Cancer-related fatigue
      b. Fatigue related to medication adverse events
      c. Fibromyalgia
      d. HIV/AIDS-related fatigue
e. Multiple sclerosis-related fatigue  
f. Myotonic Muscular Dystrophy-related hypersomnia  
g. Parkinson’s disease-related fatigue  

D. Idiopathic hypersomnia  
E. Jet-Lag disorder  
F. Obstructive sleep apnea/hypopnea without the use of CPAP or BiPAP  
G. Schizophrenia or schizoaffective disorder  
H. Use in any indication at doses exceeding 400 mg daily

Position Statement

Summary  
- Modafinil and armodafinil are both used to improve alertness, reduce tiredness, and improve memory in patients with narcolepsy, obstructive sleep apnea treated with continuous positive airway pressure (CPAP) therapy, and for patients who work nights and are tired during waking hours despite adequate sleep (shift-work sleep disorder). [1,2]  
- The studies for both medications have flaws that result in uncertainty about their conclusions.  
- The quality of the evidence for modafinil and armodafinil is comparable to other treatments, such as amphetamine and methylphenidate.  
- Modafinil (Provigil) and armodafinil (Nuvigil) contain the same active ingredient, but in different amounts. A 300 mg tablet of Provigil delivers the same amount of armodafinil as 150 mg of Nuvigil. [1,2]  
- Neither modafinil nor armodafinil correct the underlying reason for the patient’s lack of restorative sleep. Rather, both medications help treat the symptoms of tiredness and fatigue. When possible, correcting the source of the sleep problems is the preferred approach, though for some diseases (e.g. narcolepsy), this may not be possible. [1,2]  
- Despite being generically available, the cost of modafinil (generic) is similar to the branded product and therefore does not provide the best value at this time.

Clinical Efficacy

NARCOLEPSY/SLEEP APNEA/HYPOPNEA  
- Modafinil improves daytime wakefulness in patients with narcolepsy and obstructive sleep apnea/hypopnea. [3-7]  
- There is no evidence that modafinil has superior clinical benefit over other treatment alternatives, such as methylphenidate or dextroamphetamine in narcolepsy.  
- There is not conclusive evidence of additional benefit with 400 mg modafinil daily compared to 200 mg daily in patients with narcolepsy or sleep/apnea hypopnea. [3-7]
In the management of obstructive sleep apnea/hypopnea, modafinil and armodafinil should be used in ADDITION to standard treatment(s) for the underlying obstruction. If the appropriate treatment is continuous positive airway pressure (CPAP), then treatment with CPAP should be optimized before initiating either medication. [8, 9]

- There are no well-designed trials of adequate power to support additional clinical benefits of doses above 400 mg per day for the treatment of narcolepsy or sleep apnea/hypopnea.
  
  * A split-dosing modafinil regimen (400 mg in the morning; 200 mg at midday) has been evaluated in a small study (n=24) of limited duration. [10]
  
  * Another trial evaluated 4 regimens including 400 mg (200 mg am, 200 mg noon) and 600 mg (400 mg am, 200 mg noon) split dose regimens. [11] Both the 400 mg and 600 mg regimens were more effective than 200 mg once daily (p<0.01), but were not significantly different from each other. [11]

- In a 6-week study of pediatric patients (ages 5 to 17 years) with narcolepsy, there was no statistically significant differences favoring modafinil over placebo for prolonging sleep latency as measured by the MSLT. [1]

**SHIFT-WORK SLEEP DISORDER**

- Planned sleep schedules and timed-light exposure are non-drug therapies deemed as indicated for the treatment of shift-work sleep disorder by the American Academy of Sleep Medicine. [12]

- Modafinil modestly improves sleep latency and subjective reports of sleepiness when administered to patients with shift-work sleep disorder diagnosed according to criteria stipulated in the International Classification of Sleep Disorders. [1, 12-14]
  
  * After receiving modafinil 200 mg each work day for 3 months, sleep latency (measured in a sleep lab) was increased by 1.3 minutes from baseline compared to those patients receiving placebo. [12]
  
  * Of the patients taking modafinil, 74% were rated as at least minimally improved on the Clinical Global Impression of Change test at the final visit, as compared with 36 % in the placebo group. [12]

- There have been no reliable clinical trials evaluating modafinil in patients with shift-work sleep disorder that have demonstrated improved efficacy or safety with doses higher than 200 mg daily.

- Preliminary studies have suggested that modafinil 200 mg to 400 mg has about the same effect on sleep latency in patients with shift-work sleep disorder as caffeine 600 mg, though larger, well controlled trials are needed to confirm these results. [12, 15-18]

**ATTENTION DEFICIT/HYPERACTIVITY DISORDER**

- Although there are a few small, promising studies and case reports in the medical literature, there are no definitive, well-developed, adequately powered studies demonstrating the superiority of modafinil to FDA approved therapies in the treatment of attention deficit/hyperactivity disorder.
of ADHD. Therefore, the use of modafinil for ADHD is considered not medically necessary.

- Data from randomized, placebo-controlled trials indicate that treatment with modafinil in doses of 325 mg and 425 mg once daily (some dosage strengths not yet available) may improve ADHD symptoms in children ages 6 to 17 over a study period of up to 9 weeks. [19, 20-24]

- There is no evidence that differentiates safety and efficacy of modafinil from other traditional medications used for ADHD in children (such as methylphenidate or dextroamphetamine).

- While small preliminary trials have shown potential efficacy of modafinil in adults with attention deficient hyperactivity disorder [25, 26], positive results have not been demonstrated in larger, adequately-powered studies. [19]

- On March 25, 2006, the Psychopharmacologic Drugs Advisory Committee voted unanimously that modafinil (to be marketed under the trade name of Sparlon®) is effective for its intended use but recommended that Cephalon collect additional data to support the safety of the drug in children and adolescents with ADHD. [27]

  * The committee noted that in the safety database submitted by Cephalon, there were two cases of confirmed erythema multiforme, Stevens-Johnson, and 10 other possible cases of a significant rash. This would indicate a total range of risk of between 0.2% and 1.3%. [27]

AMPHEATMINE/ ALCOHOL DEPENDENCE

- A systematic review of psychostimulants (including modafinil) in amphetamine dependent patients did not show modafinil reduced amphetamine use. [28]

- A small trial (N = 83) evaluating modafinil for improved cognition in alcohol dependent patients showed mixed results. [29]

- Larger, well controlled trials are needed to establish the efficacy of modafinil in these conditions.

AUGMENTATION IN DEPRESSION

- Modafinil did not achieve study endpoints to determine its overall clinical benefit in augmenting antidepressant treatment in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. [30]

  * There was significant improvement in CGI-I (Clinical Global Impressions-Improvement). (p=0.02)

  * There were no significant differences between modafinil and placebo in improving fatigue (based on Fatigue Severity Score, Brief Fatigue Inventory) or depression (HAM-D scores, MADRS scores) after 8 weeks of treatment.

- The effectiveness of modafinil in excessive sleepiness and fatigue after SSRI treatment in patients with major depression was evaluated in a 12-week, open-label, extension study. The study experienced a high rate of drop-outs (24%) making the results of the trial unreliable. [31]
There are no randomized, controlled trials that evaluate the safety or effectiveness of modafinil used to treat manic-depressive (bipolar) disorder. Long-term safety of modafinil in this condition is unknown.

The use of modafinil in 66 patients with DSM-IV atypical major depression was assessed over 12 weeks of open-label treatment followed by a 12 week double-blind, randomized, placebo-controlled relapse phase. A significant improvement in HAM-D-29 was noted at the end of the open-label phase, but no statistically significant difference was noted at the end of the relapse phase, casting doubt on the overall efficacy of modafinil in this indication. [32]

CANCER-RELATED FATIGUE
- In a large, placebo-controlled, randomized study, 867 cancer patients with self-reported fatigue were randomized to receive either modafinil 200 mg daily or placebo. After receiving treatment for cycles 2 through 4 of their chemotherapy regimen, the results suggested some benefit to patients with severe baseline fatigue. However, failure to include all randomized patients in the analysis of the results of this trial makes the results not useful. [33]
- Other small, placebo-controlled, randomized trials showed no statistically significant difference in cancer-related fatigue in patients taking modafinil. [34-36]

HIV/AIDS-RELATED FATIGUE
- In a small, short-term, randomized, placebo-controlled trial in 115 patients with fatigue related to HIV/AIDS, modafinil appeared to improve patient-reported symptoms of fatigue and drowsiness. [37]
- While suggestive of an effect, the controlled portion of the trial lasted only four weeks, and it is unclear if the long-term effect observed during the open-label follow-on period was due to the medication or other confounding factors. [37]
- A longer controlled trial is needed to establish any long-term benefits with modafinil in HIV/AIDS related fatigue.

MULTIPLE SCLEROSIS
- Although initial studies with modafinil were promising, [38,39] new data show modafinil 100-400 mg daily is not effective in improving fatigue associated with multiple sclerosis.[40]
- Studies with armodafinil are limited to a single-dose study that concluded armodafinil did improve fatigue associated with multiple sclerosis. [41]

MYOTONIC MUSCULAR DYSTROPHY-RELATED HYPERSONMIA
- A small, short-term, randomized, double-blind, placebo-controlled trial evaluated the effect of modafinil on hypersomnia in 28 adults with myotonic muscular dystrophy type 1 (MMD1). [42]
At the end of 4 weeks, no significant effects on daytime somnolence were detected. A larger, longer-term controlled trial may be needed to find a significant effect from modafinil in this disease state. [42]

PARKINSON’S DISEASE FATIGUE

- The effect of modafinil on fatigue experienced by patients with Parkinson’s disease was explored in two small clinical studies. While these two trials were suggestive of an effect, it is not clear that modafinil resulted in substantial clinical improvement. Larger, better designed clinical trials are needed to establish clinical efficacy and safety of modafinil in this setting. [43, 44]

IDIOPATHIC HYPERSOMNIA

- There is insufficient evidence to establish the efficacy of modafinil for idiopathic hypersomnia. Only two small trials have been published to date evaluating modafinil in patients with idiopathic hypersomnia. [45, 51] Although the preliminary evidence is promising, larger, well controlled trials are needed to establish the safety and efficacy of modafinil for idiopathic hypersomnia.

JET LAG DISORDER

- The effect of armodafinil in 427 patients experiencing drowsiness after eastward travel through 6 time zones was studied in a double-blind, randomized, placebo controlled trial. [46]

- Armodafinil at a dose of 150 mg daily improved sleep latency by 6.9 minutes compared with placebo as well as improving the subjects perception of the severity of their jet lag symptoms. [46]

- It is unclear how this modest effect translates into an improvement in net health outcomes.

SCHIZOPHRENIA/ SCHIZOAFFECTIVE DISORDER

- In several small trials, the use of modafinil (100 mg to 200 mg per day) in subjects with DSM-IV schizophrenia or schizoaffective disorder did not produce a statistically significant change in the negative symptoms of schizophrenia (e.g. excessive daytime sleepiness, cognition, and psychiatric symptoms) when compared with placebo over a period of 8 weeks. [47, 48]

OTHER INDICATIONS

- The use of modafinil (400 mg per day) in 36 patients with post-polio syndrome did not produce statistically significant changes to fatigue or quality of life when compared to placebo over a period of 6 weeks. [49]

- There is insufficient evidence to support the use of modafinil or armodafinil for excessive sleepiness associated with traumatic brain injury. [52] The evidence is limited to one small trial of armodafinil, with less than 50 patients per treatment arm. Larger trials
are needed to establish the safety and efficacy of modafinil or armodafinil for this indication.

**Safety**

- The most commonly observed adverse events (>5%) associated with the use of modafinil more frequently than placebo-treated patients in the placebo-controlled clinical studies in primary disorders of sleep and wakefulness were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia. The adverse event profile was similar across these studies. [1]
- Rare but severe skin disorders such as erythema multiforme and Stevens-Johnson syndrome have been reported in patients receiving modafinil (see above). [27]
- The abuse potential of modafinil (200, 400, and 800 mg) was assessed relative to methylphenidate (45 mg and 90 mg) in an inpatient study in individuals experienced with drugs of abuse. Results from this clinical study demonstrated that modafinil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). [1, 2]

**Dosing**

- The recommended dose of modafinil is 200 mg to 400 mg orally once daily. [1]
- The safety and effectiveness of higher doses have not been established.
- For excessive daytime sleepiness due to shift-work sleep disorder, the safety and effectiveness of doses higher than 200 mg orally once daily have not been established.

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<th>Appendix 1: Diagnostic criteria for Narcolepsy [50]</th>
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<td><strong>A.</strong> Irresistible attacks of refreshing sleep that occur daily over at least 3 months.</td>
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<td><strong>B.</strong> The presence of one or both of the following:</td>
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<td>1. Cataplexy (i.e., brief episodes of sudden bilateral loss of muscle tone, most often in association with intense emotion).</td>
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<td><strong>OR</strong></td>
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<td>2. Recurrent intrusions of elements of rapid eye movement (REM) sleep into the transition between sleep and wakefulness, as manifested by either hypnopompic (i.e., the intermediate consciousness that precedes complete awakening from sleep) or hypnagogic (i.e., the state of intermediate consciousness preceding onset of sleep) hallucinations or sleep paralysis at the beginning or end of sleep episodes.</td>
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<td><strong>AND</strong></td>
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<td><strong>C.</strong> The disturbance is not due to the direct physiological effects of substance (e.g., a drug of abuse, a medication) or another general medical condition.</td>
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Appendix 2: Diagnostic Criteria: Shift Work Sleep Disorder [13]

A. There is a complaint of insomnia or excessive sleepiness that is temporally associated with a recurring work schedule that overlaps the usual time for sleep.

AND

B. The symptoms are associated with the shift-work schedule over the course of at least one month.

AND

C. Sleep log or other monitoring (with sleep diaries) for at least seven days demonstrates disturbed circadian and sleep-time misalignment.

AND

D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Cross References

Nuvigil®, armodafinil, Medication Policy Manual, dru185

Xyrem®, sodium oxybate, Medication Policy Manual, dru093

Codes

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References


