



Medication Policy Manual

Policy No: dru185

Topic: Nuvigil[®], armodafinil

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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

Armodafinil (Nuvigil[®]) is a medication used to treat excessive sleepiness. Armodafinil has wake promoting actions like amphetamines and caffeine, although the exact way armodafinil works in the body is unknown.

Policy/Criteria

I. Most contracts require prior authorization approval of armodafinil prior to coverage. Armodafinil may be considered medically necessary in patients when criteria A, B, or C below are 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. Regence considers armodafinil to be a self-administered medication.

- B. When prior authorization is approved, armodafinil may be authorized in quantities of 30 tablets per month.
- 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 compliant on CPAP while on armodafinil.
 - b. **Continued authorization:** After initial approval, authorization shall be reviewed at least annually to confirm that the patient continues to be compliant on CPAP while on armodafinil.
 - 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. Armodafinil is considered not medically necessary when used for treatment of attention deficit/hyperactivity disorder (ADHD) (pediatric or adult).

IV. Armodafinil is considered investigational when used for all other conditions, including, but not limited to, the following:

- A. Augmentation in patients with major depressive disorder.
- B. 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
- C. Idiopathic hypersomnia
- D. Jet-Lag disorder

- E. Schizophrenia or schizoaffective disorder
- F. Use in any indication at doses exceeding 250 mg daily

Position Summary

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]

Clinical Efficacy

NARCOLEPSY/SLEEP APNEA/HYPOPNEA

- Armodafinil improves daytime wakefulness in patients with narcolepsy and obstructive sleep apnea/hypopnea.^[1-3-6]
- There is no evidence that armodafinil has superior clinical benefit over other treatment alternatives, such as methylphenidate or dextroamphetamine in narcolepsy.
- There is no evidence that armodafinil has superior clinical benefit over modafinil in the treatment of narcolepsy or sleep apnea, or in any other indication.
- Armodafinil in doses up to 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose is more effective than 150 mg per day.^[1-3-6]
- 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.

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. ^[8]
- Armodafinil 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, 11, 13]
 - * After receiving armodafinil 150 mg each work day for 3 months, sleep latency (measured in a sleep lab) was increased by 2.7 minutes from baseline compared to those patients receiving placebo. ^[1, 11, 13]
 - * Of the patients taking armodafinil, 79% were rated as at least minimally improved on the Clinical Global Impression of Change test at the final visit, as compared with 59% in the placebo group. ^[1, 11, 13]
- There have been no reliable clinical trials evaluating armodafinil in patients with shift-work sleep disorder that have demonstrated improved efficacy or safety with doses higher than 150 mg daily. ^[1, 11, 13]

ATTENTION DEFICIT/HYPERACTIVITY DISORDER

- 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. ^[10, 35-39]
- 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 ^[3], positive results have not been demonstrated in larger, adequately-powered studies. ^[10]
- 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. ^[25]
 - * 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%. ^[25]

IDIOPATHIC HYPERSOMNIA

- Only one trial has been published to date evaluating modafinil in patients with idiopathic hypersomnia. ^[12]
 - * Following treatment with modafinil at 200 to 500 mg/day in two divided doses, 18 subjects with idiopathic hypersomnia experienced a statistically significant improvement in subjective drowsiness and number of sleep attacks per day. ^[12]
 - * This study had no comparator group, no placebo control, and no evaluation of functional status after treatment. This study is suggestive, but a blinded, randomized controlled trial is needed to establish efficacy in this disorder.

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. ^[14]
- 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. ^[14]
- It is unclear how this modest effect translates into an improvement in net health outcomes.

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. ^[15]

FATIGUE RELATED TO HIV/AIDS

- 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. ^[16,17]
- 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. ^[16,17]
- A longer controlled trial is needed to establish any long-term benefits with modafinil in HIV/AIDS related fatigue.

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. ^[19]

HYPERSOMNIA ASSOCIATED WITH MYOTONIC MUSCULAR DYSTROPHY

- 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). ^[18]
- 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. ^[18]

Safety

- In the placebo-controlled clinical studies, the most commonly observed adverse events ($\geq 5\%$) associated with the use of armodafinil occurring more frequently than in the placebo-treated patients were headache, nausea, dizziness, and insomnia. The adverse event profile was similar across the studies. ^[1,11]
- Serious or life threatening rash, including Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), has been reported in adults and children taking modafinil, a racemic mixture of S and R modafinil (the latter is armodafinil, the active ingredient in Nuvigil). ^[1,11]
- Although the abuse potential of armodafinil has not been specifically studied, its abuse potential is likely to be similar to that of modafinil, since modafinil contains armodafinil. ^[1,2]
- The abuse potential of modafinil (200, 400, and 800 mg) was assessed relative to methylphenidate (45 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]

Appendix 1: Diagnostic criteria for Narcolepsy ^[10]

A. Irresistible attacks of refreshing sleep that occur daily over at least 3 months.

AND

B. The presence of one or both of the following:

- 1.** Cataplexy (i.e., brief episodes of sudden bilateral loss of muscle tone, most often in association with intense emotion).

OR

- 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 proceeds 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.

AND

C. 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.

Appendix 2: Diagnostic Criteria: Shift Work Sleep Disorder ^[7]

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
Xyrem [®] , sodium oxybate dru093
Provigil [®] , armodafinil dru058

Codes	Number	Description
N/A		

References

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