PRIOR AUTHORIZATION POLICY

POLICY: Wakefulness-Promoting Agents – Armodafinil, Modafinil
- Nuvigil® (armodafinil tablets – Cephalon, generics)
- Provigil® (modafinil tablets – Cephalon, generics)

DATE REVIEWED: 08/21/2019; selected revision 03/25/2020 and 5/20/2020

OVERVIEW

Armodafinil and modafinil, agents with wake-promoting actions that are similar to sympathomimetic agents (e.g., amphetamine and methylphenidate), are indicated to improve wakefulness in adults with excessive sleepiness associated with narcolepsy; obstructive sleep apnea/hypoapnea syndrome (approved as adjunctive therapy); and shift work sleep disorder.[1,2] Armodafinil and modafinil are Schedule IV controlled substances. Review of the medical literature notes many other uses of modafinil that are considered off-label or investigational. While armodafinil has not been studied off-label to the same extent as modafinil, it is expected that armodafinil will have similar clinical efficacy for these uses.

Guidelines

According to the American Academy of Sleep Medicine, CPAP is the most uniformly effective therapy, and, to date, this is the only intervention for obstructive sleep apnea (OSA) shown to have favorable impacts on both cardiovascular and neurobehavioral morbidities.[3] Modafinil, in patients compliant with nasal CPAP, consistently improved subjective and objective sleepiness, quality of life, and vigilance compared with placebo.

According to the American Psychiatric Association (APA) practice guideline for the treatment of patients with major depressive disorder (MDD), modafinil (or methylphenidate) are potential treatments for sedation associated with antidepressant medications.[4] 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 is no clear guidance regarding the length of time modafinil should be coadministered. Limited data have investigated modafinil as monotherapy for depression.[5] While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition.

Guidelines from the AASM, updated in 2007, state that modafinil may be effective for the treatment of daytime sleepiness due to PD.[14] A practice parameter on the treatment of nonmotor symptoms of PD, published by the American Academy of Neurology (AAN) in 2011, states that for patients with PD and excessive daytime sleepiness (EDS), modafinil is effective in improving patients' perception of wakefulness, but is ineffective in objectively improving EDS as measured by objective tests.[17] 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.

Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin, updated in 2007 by the AASM, state that modafinil may be effective for the treatment of daytime sleepiness due to MS.[14] 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.

Idiopathic hypersomnia, a condition similar to narcolepsy, is characterized by constant or recurrent daytime sleepiness with no other cause of sleepiness, prolonged nocturnal sleep, difficulty awakening with sleep drunkenness, and long unrefreshing naps with no history of cataplexy.[29-32] The practice parameters for the treatment of narcolepsy and other hypersomnias of central origin, updated in 2007, state that modafinil may be effective for the treatment of daytime sleepiness due to idiopathic hypersomnia.[14] 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.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nuvigil (brand and generic) and Provigil (brand and generic). All approvals are provided for 1 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nuvigil (brand and generic) and Provigil (brand and generic) are recommended in those who meet one of the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea/Hypoapnea Syndrome.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** The patient is ≥ 18 years of age; AND
   - **B)** The patient meets one of the following criteria (i or ii):
     - **i.** Armodafinil/modafinil will be used in conjunction with continuous positive airway pressure (CPAP); OR
     - **ii.** The patient is unable to initiate or tolerate CPAP therapy; AND
   - **C)** If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
     - **i.** The patient has tried generic modafinil or generic armodafinil; AND
     - **ii.** The brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

2. **Excessive Sleepiness Associated with Shift Work Sleep Disorder.** Approve for 1 year if the patient meets the following criteria (A, B and C):
   - **A)** The patient is ≥ 18 years of age; AND
   - **B)** The patient works at least five overnight shifts per month; AND
   - **C)** If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
     - **i.** The patient has tried generic modafinil or generic armodafinil; AND
     - **ii.** The brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and

the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

3. **Excessive Daytime Sleepiness Associated with Narcolepsy.** Approve for 1 year if the patient meets both of the following criteria (A, B and C):
   A) The patient is ≥ 18 years of age; AND
   B) Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT); AND
   C) If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
      i. The patient has tried generic modafinil or generic armodafinil; AND
      ii. The brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

Other Uses with Supportive Evidence

4. **Adjunctive/Augmentation Treatment for Depression in Adults.** Approve for 1 year if the patient meets the following criteria (A, B and C):
   A) The patient is ≥ 18 years of age; AND
   B) The patient is concurrently receiving other medication therapy for depression (e.g., selective serotonin reuptake inhibitors [SSRIs]); AND
   C) If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
      i. The patient has tried generic modafinil or generic armodafinil; AND
      ii. The brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

5. **Excessive Daytime Sleepiness Associated with Myotonic Dystrophy.** Approve for 1 year if the patient meets both of the following criteria (A and B):
   A) The patient is ≥ 18 years of age; AND
   B) If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
      i. The patient has tried generic modafinil or generic armodafinil; AND
      ii. The brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

6. **Excessive Daytime Sleepiness Associated with Parkinson's Disease.** Approve for 1 year if the patient meets both of the following criteria (A and B):
   A) The patient is ≥ 18 years of age; AND
   B) If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
      i. The patient has tried generic modafinil or generic armodafinil; AND

ii. The brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction

7. **Fatigue Associated with Multiple Sclerosis (MS).** Approve for 1 year if the patient meets both of the following criteria (A and B):
   A) The patient is ≥ 18 years of age; AND
   B) If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
      i. The patient has tried generic modafinil or generic armodafinil; AND
      ii. The brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

8. **Idiopathic Hypersomnia.** Approve for 1 year if the patient meets both of the following (A, B and C):
   A. The patient is ≥ 18 years of age; AND
   B. The diagnosis is confirmed by a sleep specialist physician or at an institution that specializes in sleep disorders (i.e., sleep center); AND
   C. If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
      i. The patient has tried generic modafinil or generic armodafinil; AND
      ii. The brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Nuvigil and Provigil (brand and generic) have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Attention Deficit Hyperactivity Disorder (ADHD).** The American Academy of Pediatrics (AAP) clinical practice guidelines for the treatment of ADHD in children and adolescents (2011) does not address the use of modafinil/armodafinil.[43,44] These guidelines note that with the greater availability of approved medications for children/adolescents with ADHD, it has become increasingly unlikely that clinicians need to consider the off-label use of other medications. Two published studies, both of which involved approximately 20 adult patients with ADHD, preliminarily suggested that modafinil may be useful for this condition.[45,49] However, a 9-week, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study in adults with ADHD (n = 338) evaluated modafinil doses of 255 mg to 510 mg and did not find significant benefit in reducing ADHD symptoms, as measured by the change from baseline at final visit in the Adult ADHD Investigator Symptom Rating Scale (AISRS) total score.[47] Many options exist for the treatment of ADHD in adults (e.g., methylphenidate, dextroamphetamine) and further large scale trials that demonstrate benefit for modafinil in adults with ADHD are needed.

2. **Bipolar Disorder, including Bipolar Depression.** Limited data (one small study [n = 85] and case reports [n = 2]) are available that describe the use of modafinil for bipolar disorder and bipolar depression.[48-50] In one study (n = 257) armodafinil was not more effective than placebo in treating bipolar depression.[51] Only limited data supports modafinil for this condition and more data are needed.

3. **Cancer-Related Fatigue.** The National Comprehensive Cancer Network (NCCN) guidelines on cancer-related fatigue (version 1.2019 – March 12, 2019) no longer consider modafinil to be effective for the treatment of cancer-related fatigue and recommend against its use.[28] A randomized, double-blind, placebo-controlled trial involving 631 patients with cancer receiving chemotherapy found modafinil useful in the control of severe cancer-related fatigue only.[7] Other studies do not support the use of modafinil or armodafinil for cancer-related fatigue.[69-72]

4. **Chronic Fatigue Syndrome.** Limited data characterize modafinil therapy in those with chronic fatigue syndrome.[52,53] In a randomized, double-blind, crossover study in 14 patients with chronic fatigue syndrome, use of modafinil for 20 days had minimal effects on cognitive function and no significant effects on fatigue, health-related quality of life, or mood.[70] More data are required to assess efficacy in this patient population.

5. **Excessive Daytime Sleepiness Associated with Primary Insomnia.** One randomized, placebo-controlled study found that neither combination therapy with modafinil and cognitive behavioral therapy nor modafinil as monotherapy significantly decreased daytime sleepiness associated with primary insomnia.[54]

6. **Enhancement of Performance in Situations of Induced Sleep Deprivation.** Studies are needed to define the role/appropriateness of modafinil in these situations for the general population (as opposed to military personnel, etc.). Studies have shown that modafinil may enhance performance and sustain alertness in individuals subjected to situations that deprive sleep (e.g., military aviation, emergency physicians).[55-58] Further studies are needed before its use in the general population in these types of situations can be promoted.

7. **Fatigue and Excessive Daytime Sleepiness in Chronic Traumatic Brain Injury (TBI).** A single-center, double-blind, placebo- controlled, crossover trial involving 53 patients suggests that overall, modafinil was not beneficial in relieving fatigue and EDS in such patients.[59] In a small (n = 20) randomized, placebo-controlled trial, modafinil improved EDS vs. placebo in patients with TBI; however, modafinil did not improve fatigue compared with placebo.[60] Additional data are needed to determine effectiveness in this setting.

8. **Fibromyalgia.** Limited data are available regarding the use of modafinil in fibromyalgia with most of the data being observational.[61-63] Larger-sized, randomized, placebo-controlled trials are required to better assess and validate the efficacy of modafinil in patients with fibromyalgia before it can be recommended as a therapeutic modality.

9. **Hypersomnia, Fatigue or Sleepiness Due to Other Conditions (<u>not</u> Idiopathic Hypersomnia, see Other Uses with Supportive Evidence).** More data are needed in specific conditions to define the role of modafinil and armodafinil.

10. **Post-Stroke Sleep-Wake Disorders or Sleep Disorders.** Sleep-wake disorders occur in approximately 20% to 40% of patients that have experienced a stroke, which includes hypersomnia and EDS. Very limited data (i.e., case reports and one small study) have explored the use of modafinil in

these patients to improve alertness.[64,73] More data are needed to determine effectiveness in this condition.

11. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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