NUVIGIL® (armodafinil) tablets, for oral use, C-IV

1 INDICATIONS AND USAGE

NUVIGIL is indicated to improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnea (OSA), narcolepsy, or shift work disorder (SWD). [1] Limitations of Use

In OSA, NUVIGIL is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction.

2 DOSAGE AND ADMINISTRATION

The recommended dosage of NUVIGIL for each indication is as follows:

- OSA or Narcolepsy: 150 mg to 250 mg once a day in the morning. [2.1]
- SWD: 150 mg once a day, taken approximately one hour prior to the start of the work shift. [2.2]
- Hepatic Impairment: reduced dose in patients with severe hepatic impairment. [2.3, 12.3]
- Geriatric Patients: consider lower dose. [2.4, 12.3]

3 DOSAGE FORMS AND STRENGTHS

 Tablets: 50 mg, 150 mg, 200 mg, and 250 mg. [3]

4 CONTRAINDICATIONS

NUVIGIL is contraindicated in patients with known hypersensitivity to modafinil or armodafinil. [4]

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Warnings and Precautions

- Serious Rash, including Stevens-Johnson Syndrome: discontinue NUVIGIL at the first sign of rash, unless the rash is clearly not drug-related. [5.1]
- DRESS/Multi-organ Hypersensitivity Reactions: if suspected, discontinue NUVIGIL. [5.2]
- Angioedema and Anaphylaxis Reactions: if suspected, discontinue NUVIGIL. [5.3]
- Persistent Sleepiness: assess patients frequently for degree of sleepiness and, if appropriate, advise patients to avoid driving or engaging in any other potentially dangerous activity. [5.4]
- Psychiatric Symptoms: use particular caution in treating patients with a history of psychosis, depression, or mania. Consider discontinuing NUVIGIL if psychiatric symptoms develop. [5.5]
- Known Cardiovascular Disease: consider increased monitoring. [5.7]

Adverse Reactions

Most common adverse reactions (≥5%): headache, nervousness, dizziness, and insomnia. [6.1]

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-800-896-5855 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Drug Interactions

- Steroidal contraceptives (e.g., ethinyl estradiol): use alternative or concomitant methods of contraception while taking NUVIGIL and for one month after discontinuation of NUVIGIL treatment. [7]
- Cyclosporine: blood concentrations of cyclosporine may be reduced. [7]
- CYP2C19 substrates, such as omeprazole, phenytoin, and diazepam: exposure of these medications may be increased. [7]

Use in Specific Populations

Pregnancy: based on animal data, may cause fetal harm. [8.1]

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*Sections or subsections omitted from the full prescribing information are not listed.
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NUVIGIL has not been studied in pediatric patients in any setting and is not approved for use in pediatric patients for any indication.

In clinical trials of modafinil, the incidence of rash resulting in discontinuation was approximately 0.8% (13 per 1,585) in pediatric patients (age <17 years); these rashes included 1 case of possible Stevens-Johnson syndrome (SJS) and 1 case of apparent multi-organ hypersensitivity reaction/Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) [see Warnings and Precautions (5.2)]. Several of the cases were associated with fever and other abnormalities (e.g., vomiting, leukopenia). The median time to rash that resulted in discontinuation was 13 days. No such cases were observed among 380 pediatric patients who received placebo.

Skin and mouth sores, blistering, and ulceration have been reported with modafinil and NUVIGIL in the postmarket setting. Recurrence of signs and symptoms of serious dermatologic reactions following rechallenge has been reported in some cases. Rare cases of serious or life-threatening rash, including SJS and toxic epidermal necrolysis (TEN), have been reported in adults and children in worldwide postmarket setting with modafinil and NUVIGIL.

There are no factors, including duration of therapy, that are known to predict the risk of occurrence or the severity of rash associated with modafinil or NUVIGIL. In cases where the time to onset was reported, serious rash occurred 1 day to 2 months after initiation of treatment, but isolated cases of serious dermatologic reactions have been reported as early as 1 week after initiation of therapy. Although benign rashes also occur with NUVIGIL, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, NUVIGIL should be discontinued at the first sign of rash, skin or mouth sores, or blistering or ulceration, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

5.2 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multorgan Hypersensitivity

DRESS, also known as multi-organ hypersensitivity, has been reported with modafinil. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocardiatis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even when rash is not evident. One fatal case of DRESS that occurred in close temporal association (3 weeks) with the initiation of NUVIGIL treatment has been reported in the postmarketing setting. In addition, multi-organ hypersensitivity reactions, including at least one fatality in postmarketing experience, have occurred in close temporal association (median time to detection 13 days, range 4-33) to the initiation of modafinil. Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalization or be life-threatening. If a multi-organ hypersensitivity reaction is suspected, NUVIGIL should be discontinued immediately. If a multi-organ hypersensitivity reaction is suspected, NUVIGIL should be discontinued immediately. Patients should be advised to discontinue NUVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. Findings suggestive of mitral valve prolapse syndrome include but are not limited to ischemic ECG changes, chest pain, or arrhythmia. If new onset of any of these findings occurs, consider cardiac evaluation.

Blood pressure monitoring in short term (≥ 3 months) pre-approval controlled trials of OSA, SWD, and narcolepsy showed small average increases in mean systolic and diastolic blood pressure in patients receiving NUVIGIL as compared to placebo (1.2 to 4.3 mmHg in the various experimental groups). There was also a slightly greater proportion of patients on NUVIGIL requiring new or increased use of antihypertensive medications (2.9%) compared to patients on placebo (1.8%). There was a small, but consistent, average increase in pulse rate over placebo in pre-approval controlled trials. This increase varied from 0.9 to 3.5 BPM. Increased monitoring of heart rate and blood pressure may be appropriate in patients on NUVIGIL. Caution should be exercised in prescribing NUVIGIL to patients with known cardiovascular disease.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

• Serious Dermatologic Reactions [see Warnings and Precautions (5.1)]

• Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multigorgan Hypersensitivity [see Warnings and Precautions (5.2)]

• Angioedema and Anaphylaxis Reactions [see Warnings and Precautions (5.3)]

• Persistent Sleepiness [see Warnings and Precautions (5.4)]

• Psychiatric Symptoms [see Warnings and Precautions (5.5)]

• Effects on Ability to Drive and Use Machinery [see Warnings and Precautions (5.6)]

• Cardiovascular Events [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. NUVIGIL has been evaluated for safety in over 1,100 patients with excessive sleepiness associated with OSA, SWD, and narcolepsy.

Most Common Adverse Reactions

In the placebo-controlled clinical trials, the most common adverse reactions (≥5%) associated with the use of NUVIGIL more frequently than in placebo-treated patients were headache, nausea, dizziness, and insomnia. The adverse reaction profile was similar across the studies. Table 1 presents the adverse reactions that occurred at a rate of 1% or more and were more frequent in NUVIGIL-treated patients than in placebo-treated patients in the placebo-controlled clinical trials.

Table 1: Adverse Reactions in Pooled Placebo-Controlled Clinical Trials* in OSA, Narcolepsy, and SWD with NUVIGIL (150 mg and 250 mg)

<table>
<thead>
<tr>
<th>NUVIGIL (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=645</td>
<td>N=445</td>
</tr>
<tr>
<td>Headache</td>
<td>17  9</td>
</tr>
<tr>
<td>Nausea</td>
<td>7  3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5  2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5  1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4  1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4  2</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>4  1</td>
</tr>
<tr>
<td>Depression</td>
<td>2  0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2  0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2  1</td>
</tr>
<tr>
<td>Palpitations</td>
<td>2  1</td>
</tr>
<tr>
<td>Rash</td>
<td>2  0</td>
</tr>
<tr>
<td>Upper Abdominal Pain</td>
<td>2  1</td>
</tr>
<tr>
<td>Agitation</td>
<td>1  0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1  0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1  0</td>
</tr>
<tr>
<td>Contact Dermatitis</td>
<td>1  0</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>1  0</td>
</tr>
<tr>
<td>Depressed Mood</td>
<td>1  0</td>
</tr>
</tbody>
</table>
NUVIGIL® (armodafinil) tablets, for oral use, C-IV

<table>
<thead>
<tr>
<th>NUVIGIL® (armodafinil) tablets, for oral use, C-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUVIGIL (mg)</td>
</tr>
<tr>
<td>Disturbance In Attention</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Hyperhydrosis</td>
</tr>
<tr>
<td>Increased Gamma-Glutamyltransferase</td>
</tr>
<tr>
<td>Increased Heart Rate</td>
</tr>
<tr>
<td>Influenza-Like Illness</td>
</tr>
<tr>
<td>Loose Stools</td>
</tr>
<tr>
<td>Migraine</td>
</tr>
<tr>
<td>Nervousness</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Paresthesia</td>
</tr>
<tr>
<td>Polypnea</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Seasonal Allergy</td>
</tr>
<tr>
<td>Thirst</td>
</tr>
<tr>
<td>Tremor</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
</tbody>
</table>

*Adverse reactions that occurred in ≥1% of NUVIGIL-treated patients and greater incidence than that of placebo.

Dose-Dependent Adverse Reactions

In the placebo-controlled clinical trials which compared doses of 150 mg/day and 250 mg/day of NUVIGIL and placebo, the following adverse reactions were dose-related: headache, rash, depression, dry mouth, insomnia, and nausea. See Table 2 for additional information.

Table 2: Dose-Dependent Adverse Reactions in Pooled Placebo-Controlled Clinical Trials in OSA, Narcolepsy and SWD

<table>
<thead>
<tr>
<th>NUVIGIL 250 mg (%)</th>
<th>N=188</th>
<th>NUVIGIL 150 mg (%)</th>
<th>N=447</th>
<th>NUVIGIL Combined (%)</th>
<th>N=645</th>
<th>Placebo (%)</th>
<th>N=445</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>23</td>
<td>14</td>
<td>17</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adverse Reactions Resulting in Discontinuation of Treatment

The following adverse reactions have been identified during post approval use of NUVIGIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Mouth Sores (including mouth blistering and ulceration)

Blood levels of cyclosporine may be reduced when used with NUVIGIL. Monitoring of circulating cyclosporine concentrations and appropriate dosage adjustment for cyclosporine should be considered when used concomitantly with NUVIGIL.

Effects of NUVIGIL on CYP2C19 Substrates

Elimination of drugs that are substrates for CYP2C19 (e.g., phenytoin, diazepam, propranolol, omeprazole, and clomipramine) may be prolonged by NUVIGIL via inhibition of metabolic enzymes, with resultant higher systemic exposure. Dose reduction of these drugs may be required when these drugs are used concomitantly with NUVIGIL.

Warfarin

More frequent monitoring of prothrombin times/INR should be considered whenever NUVIGIL is coadministered with warfarin [see Clinical Pharmacology (12.3)]. Monoamine Oxidase (MAO) Inhibitors

Caution should be used when concomitantly administering MAO inhibitors and NUVIGIL.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUVIGIL during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-866-404-4106.

Risk Summary

Limited available data on armodafinil use in pregnant women are insufficient to inform a drug associated risk of adverse pregnancy outcomes. Intrauterine growth restriction and spontaneous abortion have been reported in association with armodafinil and modafinil. Although the pharmacology of the armodafinil is not identical to that of the sympathomimetic amines, armodafinil shares some pharmacologic properties with this class [see Clinical Pharmacology (12.1)]. Some sympathomimetics have been associated with intrauterine growth restriction and spontaneous abortions.

In animal reproduction studies of armodafinil (R-modafinil) and modafinil (a mixture of R- and S-modafinil) conducted in pregnant rats, armodafinil, modafinil, and rabbits (modafinil) during organogenesis, evidence of developmental toxicity (increased embryofetal and offspring mortality, decreased fetal growth) was observed at clinically relevant plasma exposures.

All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Oral administration of armodafinil (60, 200, or 600 mg/kg/day) to pregnant rats throughout organogenesis produced an increase in resorptions and an increased incidence of fetal variations indicative of growth delay at the highest dose, which was also maternally toxic. The highest no-effect dose for embryofetal developmental toxicity in rat (200 mg/kg/day) was associated with a plasma armodafinil exposure (AUC) less than that in humans at the maximum recommended human dose (MRHD) of NUVIGIL (250 mg/day).

Modafinil (50, 100, or 200 mg/kg/day) administered orally to pregnant rats throughout organogenesis produced an increase in resorptions and an increased incidence of fetal variations at the highest dose tested. The higher no-effect dose for embryofetal developmental toxicity (100 mg/kg/day) was associated with a plasma armodafinil AUC less than that in humans at the MRHD of NUVIGIL. However, in a subsequent rat study of up to 480 mg/kg/day of modafinil, no adverse effects on embryofetal development were observed.

In a study in which modafinil (45, 90, or 180 mg/kg/day) was orally administered to pregnant rabbits during organogenesis, embryofetal death was increased at the highest dose. The highest no-effect dose for developmental toxicity (100 mg/kg/day) was associated with a plasma armodafinil AUC less than that in humans at the MRHD of NUVIGIL.

Modafinil administration to rats throughout gestation and lactation at oral doses of up to 200 mg/kg/day resulted in decreased viability in the offspring at doses greater than 20 mg/kg/day, a dose resulting in a plasma armodafinil AUC less than that in humans at the MRHD of NUVIGIL. No effects on postnatal developmental and neurobehavioral parameters were observed in surviving offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of armodafinil or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.

There is no information on the excretion of armodafinil in human milk. Because many drugs are excreted in human milk following the ingestion of NUVIGIL, and because of the potential for serious adverse reactions in the breastfed infant, a decision should be made whether to discontinue use of NUVIGIL or to discontinue breastfeeding, taking into account the importance of the drug to the mother.

8.3 Females and Males of Reproductive Potential

The effectiveness of hormonal contraceptives may be reduced when used with NUVIGIL and for one month after discontinuation of therapy. Advise women who are using a hormonal method of contraception to use an additional barrier method or an alternative non-hormonal method of contraception during treatment with NUVIGIL and for one month after discontinuation of NUVIGIL treatment [see Drug Interactions (7) and Clinical Pharmacology (12.3)].
8. **Pediatric Use**
Safety and effectiveness in pediatric patients have not been established. Serious rash has been seen in pediatric patients receiving modafinil [see Warnings and Precautions (5.1)].

8.5 **Geriatric Use**
In elderly patients, elimination of armodafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses and close monitoring in this population [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

8.6 **Hepatic Impairment**
The dosage of NUVIGIL should be reduced in patients with severe hepatic impairment [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

9 **DRUG ABUSE AND DEPENDENCE**
9.1 **Controlled Substance**
NUVIGIL contains armodafinil, a Schedule IV controlled substance.

9.2 **Abuse**
Abuse of NUVIGIL has been reported in patients treated with NUVIGIL. Patterns of abuse have included euphoric mood and use of increasingly large doses or recurrent use of NUVIGIL for a desired effect. Drug diversion has also been noted. During the postmarketing period, misuse of NUVIGIL has been observed (e.g., taking NUVIGIL against a physician’s advice, and obtaining NUVIGIL from multiple physicians).

Abuse of armodafinil, the active ingredient of NUVIGIL, poses a risk of overdose similar to that seen for modafinil, which may lead to tachycardia, insomnia, agitation, dizziness, anxiety, nausea, headache, dysoria, tremor, chest pain, hypertension, seizures, delirium, or hallucinations. Other signs and symptoms of CNS stimulant abuse include tachypnea, sweating, dilated pupils, hyperactivity, restlessness, decreased sleep, loss of coordination, flushed skin, vomiting, and abdominal pain. In humans, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings, typical of other CNS stimulants. In in vitro binding studies, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release. Modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies, modafinil was also partially discriminated as stimulant-like.

Physicians should follow patients closely, especially those with a history of drug and/or stimulant (e.g., methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (e.g., incrementation of doses or drug-seeking behavior).

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).

9.3 **Dependence**
Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Physical dependence can occur in patients treated with NUVIGIL. Abrupt cessation or dose reduction following chronic use can result in withdrawal symptoms, including shaking, sweating, chills, nausea, vomiting, confusion, aggression, and atrial fibrillation. Drug withdrawal has caused deterioration of psychiatric symptoms such as depression. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Multiple cases of development of tolerance to NUVIGIL have been reported during the postmarketing period.

10 **OVERDOSAGE**
Fatal overdoses involving modafinil alone or involving NUVIGIL or modafinil overdose, alone or in combination with other drugs, have been reported in the postmarketing setting. Symptoms most often accompanying NUVIGIL or modafinil overdose, alone or in combination with other drugs, have included anxiety, dyspnea, insomnia; central nervous system symptoms such as restlessness, disorientation, confusion, excitation and hallucination; digestive changes such as nausea and diarrhea; and cardiovascular changes such as tachycardia, bradycardia, hypertension, and chest pain.

No specific antidote exists for the toxic effects of a NUVIGIL overdose. Such overdoses should be managed with primarily supportive care, including cardiovascular monitoring.

11 **DESCRIPTION**
NUVIGIL (armodafinil) is a wakefulness-promoting agent for oral administration. Armodafinil is the R-enantiomer of modafinil which is a 1:1 mixture of the R- and S-enantiomers. The chemical name for armodafinil is 2-(R)-(diphenylmethylsulfinyl) acetamide. The molecular formula is C18H18NO2S and the molecular weight is 279.35. The chemical structure is:

![Chemical Structure](image)

Armodafinil is a white to off-white, crystalline powder that is slightly soluble in water, sparingly soluble in acetone, and insoluble in methanol. NUVIGIL tablets contain 50, 150, 200 or 250 mg of armodafinil and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and pregelatinized starch.

12 **CLINICAL PHARMACOLOGY**
12.1 **Mechanism of Action**
The mechanism(s) through which armodafinil promotes wakefulness is unknown. 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. Armodafinil and modafinil 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.

Modafinil-induced wakefulness can be attenuated by the α1-adrenergic receptor antagonist, prazosin; however, modafinil is inactive in other in vitro assay systems known to be responsive to α1-adrenergic agonists such as the rat vas deferens preparation.

Armodafinil is an indirect dopamine receptor agonist; both armodafinil and modafinil bind in vitro to the dopamine transporter and inhibit dopamine reuptake. For modafinil, this activity has been associated in vivo with increased extracellular Dopamine. In animals, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants in humans. Modafinil was also partially discriminated as stimulant-like. Based on nonclinical studies, two major metabolites, acid and sulfone, of modafinil or armodafinil, do not appear to contribute to the CNS-activating properties of the parent compounds.

12.3 **Pharmacokinetics**
Armodafinil exhibits linear time-independent kinetics following single and multiple oral dose administration. Increase in systemic exposure is proportional over the dose range of 50 to 400 mg. No time-dependent change in kinetics was observed through 12 weeks of dosing. Apparent steady state for armodafinil was reached within 7 days of dosing. At steady state, the systemic exposure for armodafinil is 1.8 times the exposure observed after a single dose. The concentration-time profiles of the R-enantiomer following administration of a single-dose of 50 mg NUVIGIL or 100 mg PROVIGIL (modafinil, a 1:1 mixture levorotatory and dextrorotatory isomers) in a 2-hour period was approximately 37% and 70% higher, respectively, following administration of 200 mg NUVIGIL than the corresponding values of modafinil following administration of 200 mg PROVIGIL due to the more rapid clearance of the S-enantiomer (elimination half-life approximately 4 hours) as compared to the R-enantiomer.

**Absorption**
NUVIGIL is readily absorbed after oral administration. The absolute oral bioavailability was not determined due to the aqueous insolubility of armodafinil, which precluded intravenous administration. Peak plasma concentrations are attained at approximately 2 hours in the fasted state. The peak plasma concentration (Cmax) of armodafinil in steady-state were approximately 37% and 70% higher, respectively, following administration of 200 mg NUVIGIL than the corresponding values of modafinil following administration of 200 mg PROVIGIL due to the more rapid clearance of the S-enantiomer (elimination half-life approximately 4 hours) as compared to the R-enantiomer.

**Distribution**
NUVIGIL has an apparent volume of distribution of approximately 42 L. Data specific to armodafinil protein binding are not available. However, modafinil is moderately bound to plasma protein (approximately 60%), mainly to albumin. The potential for armodafinil protein binding are not available. However, modafinil is moderately bound to plasma protein (approximately 60%), mainly to albumin. The protein binding of armodafinil is likely minimal; however, time to reach peak concentration (tmax) may be delayed by approximately 2-4 hours in the fed state. Since the delay in tmax is also associated with elevated plasma concentrations later in time, food can potentially affect the onset and time course of pharmacologic action for NUVIGIL.

**Metabolism**
Modafinil undergoes hydrolytic deamination, S-oxidation, and aromatic ring hydroxylation, with subsequent glucuronide conjugation of the hydroxylated products. Amide hydrolysis is the single most prominent metabolic pathway, with sulfone formation by cytochrome P450 (CYP) 3A4/5 being important in the other oxidative products are formed too slowly in vitro to enable identification of the enzyme(s) responsible. Only two metabolites reach appreciable concentrations in plasma (i.e., R-modafinil acid and modafinil sulfone).

**Excretion**
Data specific to NUVIGIL disposition are not available. However, modafinil is mainly eliminated via metabolism, predominantly in the liver, with less than 10% of the parent compound excreted in the urine. A total of 81% of the administered radioactivity was recovered in 11 days post-dose, predominantly in the urine (80% vs. 1.0% in the feces).

![Chemical Structure](image)
Concomitant administration of modafinil with methylphenidate or dextroamphetamine produced no significant alterations on the pharmacokinetic profile of modafinil or either stimulant, even though the absorption of modafinil was delayed for approximately one hour. Concomitant modafinil or clomipramine did not alter the pharmacokinetic profile of either drug; however, one incident of increased levels of clomipramine and its active metabolite desmethylclomipramine was reported in a patient with narcolepsy during treatment with modafinil.

Data specific to NUVIGIL or modafinil drug-drug interaction potential with monoamine oxidase (MAO) inhibitors are not available [see Drug Interactions (7)].

- **Interaction with P-Glycoprotein**

- **Interactions with Other Drugs**

Data specific to NUVIGIL drug-drug interaction potential for additional other drugs are not available. However, the following drug-drug interaction information on modafinil should be applicable to NUVIGIL.

Warfarin: Concomitant administration of modafinil with warfarin did not produce significant changes in the pharmacokinetic profiles of R- and S-warfarin. However, since only a single dose of warfarin was tested in this study, an interaction cannot be ruled out [see Drug Interactions (7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a mouse carcinogenicity study, armodafinil (R-modafinil) was administered at oral doses of up to 300 mg/kg/day in males and 100 mg/kg/day in females for approximately two years, no tumorigenic effects were observed. In a rat carcinogenicity study modafinil (a mixture of R- and S-modafinil) was administered at oral doses of up to 60 mg/kg/day for two years; no tumorigenic effects were observed. At the highest doses studied in mouse and rat, the plasma armodafinil exposures (AUC) were less than that in humans at the MRHD of NUVIGIL (250 mg/day).

Mutagenesis

Armodafinil was negative in an in vitro bacterial reverse mutation assay and in an in vitro chromosomal aberration assay in human lymphocytes. Modafinil was negative in a series of in vitro (i.e., bacterial reverse mutation, mouse lymphoma tk, chromosomal aberration in human lymphocytes, cell transformation in BALB/3T3 mouse embryo cells) or in vivo (mouse bone marrow micronucleus) assays.

Impairment of Fertility

A fertility and early embryonic development (to implantation) study was not conducted with modafinil alone. Oral administration of modafinil (doses of up to 480 mg/kg/day) to male and female rats prior to and throughout mating, and continuing in females through day 7 of gestation produced an increase in the time to mate at the highest dose; no effects were observed on other fertility or reproductive parameters. The no-effect dose of 240 mg/kg/day was associated with a plasma armodafinil AUC less than that in humans at the MRHD of NUVIGIL.

14 CLINICAL STUDIES

14.1 Obstructive Sleep Apnea (OSA)

The effectiveness of NUVIGIL in improving wakefulness in patients with excessive sleepiness associated with OSA in established, placebo-controlled, parallel-group, double-blind clinical studies of outpatients who met the criteria for OSA. The criteria include either: 1) excessive sleepiness or insomnia, plus frequent episodes of impaired breathing during sleep, and associated features such as loud snoring, morning headaches or dry mouth upon awakening; or 2) excessive sleepiness or insomnia; and polysomnography demonstrating one of the following: more than five obstructive apneas, each greater than 10 seconds in duration, per hour of sleep; and one or more of the following: frequent arousals from sleep associated with the apneas, bradycardia, or arterial oxygen desaturation in association with the apneas. In addition, for entry into these studies, all patients were required to have excessive sleepiness as demonstrated by a score >10 on the Epworth Sleepiness Scale (ESS), despite treatment with continuous positive airway pressure (CPAP). Evidence that CPAP was effective in reducing episodes of apnea/hypopnea was required along with documentation of CPAP use. Patients were required to be compliant with CPAP, defined as CPAP use >4 hours/night on ≥70% of nights. CPAP use continued throughout the study. In both studies, the primary measures of effectiveness were 1) sleep latency, as assessed by the Maintenance of Wakefulness Test (MWT) and 2) the change in the patient’s overall disease status, as measured by the Clinical Global Impression of Change (CGI-C) at the final visit. For a successful trial both measures had to show statistically significant improvement. The MWT measures latency (in minutes) to sleep onset. An extended MWT was performed with test sessions at 2 hour intervals between 9AM and 7PM. The primary analysis was the average of the sleep latencies from the first four test sessions (9AM to 3PM). For each test session, the subject was asked to attempt to remain awake without using extraordinary measures. Each test session was terminated after 30 minutes if no sleep occurred or immediately after sleep onset. The CGI-C is a 7-point scale, centered at No Change, and ranging from Very Much Worse to Very Much Improved. Evaluators were not given any specific guidance about the criteria they were to apply when rating patients.
In the first study, a total of 395 patients with OSA were randomized to receive NUVIGIL 150 mg/day, NUVIGIL 250 mg/day or matching placebo. Patients treated with NUVIGIL showed a statistically significant improvement in the ability to remain awake compared to placebo-treated patients as measured by the MWT at final visit. A statistically significant greater number of patients treated with NUVIGIL showed improvement in overall clinical condition as rated by the CGI-C scale at final visit. The average sleep latency measured in this study (OSA II) in the trials are shown in Table 3 below, along with the average change from baseline on the MWT at final visit.

In the second study, 263 patients with OSA were randomized to either NUVIGIL 150 mg/day or placebo. Patients treated with NUVIGIL showed a statistically significant improvement in the ability to remain awake compared to placebo-treated patients as measured by the MWT (Table 3). A statistically significant greater number of patients treated with NUVIGIL showed improvement in overall clinical condition as rated by the CGI-C scale (Table 4). Nighttime sleep measured with polysomnography was not affected by the use of NUVIGIL in either study.

### 14.2 Narcolepsy

The effectiveness of NUVIGIL in improving wakefulness in patients with excessive sleepiness associated with narcolepsy was established in one 12-week, multi-center, placebo-controlled, parallel-group, double-blind study of outpatients who met the criteria for narcolepsy. A total of 196 patients were randomized to receive NUVIGIL 150 or 250 mg/day or matching placebo. The criteria for narcolepsy included: 1) recurrent daytime naps or lapses into sleep that occur almost daily for at least three months, plus sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy); or 2) a complaint of excessive sleepiness or sudden muscle weakness with associated features: sleep paralysis, hypnagogic hallucinations, automatic behaviors, an inability to fall asleep in the middle of the night, and/or polysonomography demonstrating one of the following: sleep latency less than 10 minutes or rapid eye movement (REM) sleep latency less than 20 minutes and a Multiple Sleep Latency Test (MSLT) that demonstrates a mean sleep latency of less than 5 minutes and two or more sleep onset REM periods and no medical or mental disorder accounts for the symptoms. Following into these studies, all patients were required to have objectively documented excessive daytime sleepiness, via MSLT with a sleep latency of 6 minutes or less and the absence of any other clinically significant active medical or psychiatric disorder. The MSLT, an objective polysomnographic assessment of the patient’s ability to fall asleep in an unsimulating environment, measured latency (in minutes) to sleep onset average over four 20-minute intervals. For each test session, the subject was told to lie quietly and attempt to sleep. Each test session was terminated after 20 minutes if no sleep occurred or immediately after sleep onset.

The primary measures of effectiveness were: 1) sleep latency as assessed by the Maintenance of Wakefulness Test (MWT), and 2) the change in the patient’s overall disease status, as measured by the CGI-C at the final visit (see Clinical Studies (14.1) for a description of these measures). Each MWT test session was terminated after 20 minutes if no sleep occurred or immediately after sleep onset in this study.

Patients treated with NUVIGIL showed a statistically significantly enhanced ability to remain awake compared to placebo at final visit (Table 3). A statistically significant greater number of patients treated with NUVIGIL at each dose showed improved in overall clinical condition as rated by the CGI-C scale at final visit (Table 4).

The two doses of NUVIGIL produced statistically significant effects of similar magnitude on the CGI-C, although a statistically significant effect on the MWT was observed for each dose, the magnitude of effect was observed to be greater for the higher dose. Nighttime sleep measured with polysomnography was not affected by the use of NUVIGIL.

### 14.3 Shift Work Disorder (SWD)

The effectiveness of NUVIGIL in improving wakefulness in patients with excessive sleepiness associated with SWD was demonstrated in a 12-week, multi-center, double-blind, placebo-controlled, parallel-group clinical trial. A total of 254 patients with chronic SWD were randomized to receive NUVIGIL 150 mg/day or placebo. All patients were stratified for chronic SWD. This study included: 1) a primary complaint of excessive sleepiness or insomnia which is temporally associated with a work period (usually night work) that occurs during the habitual sleep phase, or b) polysomnography and the MSLT demonstrate loss of a normal sleep-wake pattern (i.e., disturbed chronobiological rhythmicity); and 2) no other medical or mental disorder accounts for the symptoms; and 3) the symptoms do not meet criteria for any other sleep disorder producing insomnia or excessive sleepiness (e.g., time zone change [jet lag] syndrome).

It should be noted that not all patients with a complaint of sleepiness who are also engaged in shift work meet the criteria for the diagnosis of SWD. In the clinical trial, only patients who were symptomatic for at least 3 months were enrolled. Enrolled patients were also required to work a minimum of 5 night shifts per month, have excessive sleepiness at the time of their night shifts (MSLT score ≥6 minutes), and have daytime insomnia documented by a daytime polysomnogram.

The primary measures of effectiveness were: 1) sleep latency, as assessed by the Multiple Sleep Latency Test (MSLT) performed during a simulated night shift at the final visit; and 2) the change in the patient’s overall disease status, as measured by the CGI-C at the final visit (see Clinical Studies (14.1) for a description of these measures).
NUVIGIL® (armodafinil) tablets, for oral use, C-IV

Medication Guide
NUVIGIL (nu-vij-el)
(armodafinil)
tables, for oral use, C-IV

What is the most important information I should know about NUVIGIL?
NUVIGIL is a federal controlled substance (C-IV) because it can be abused or lead to dependence. Keep NUVIGIL in a safe place to prevent misuse and abuse. Selling or giving away NUVIGIL may harm others, and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.

NUVIGIL may cause serious side effects including a serious rash or a serious allergic reaction that may affect parts of your body such as your liver or blood cells. Any of these may need to be treated in a hospital and may be life-threatening.

Stop taking NUVIGIL and call your doctor right away or get emergency help if you have any of these symptoms:
- skin rash, hives, sores in your mouth, or your skin blisters and peels
- swelling of your face, eyes, lips, tongue, or throat
- trouble swallowing, breathing, or hoarseness
- fever, shortness of breath, swelling of the legs, yellowing of the skin or whites of the eyes, or dark urine.

If you have a severe rash with NUVIGIL, stopping the medicine may not keep the rash from becoming life-threatening or causing you to be permanently disabled or disfigured.

NUVIGIL is not approved for use in children for any medical condition.
It is not known if NUVIGIL is safe and effective in children under the age of 18.

What is NUVIGIL?
NUVIGIL is a prescription medicine used to improve wakefulness in adults who are very sleepy due to one of the following diagnosed sleep disorders:
- narcolepsy

Psychiatric Symptoms
Advise patients to stop taking NUVIGIL and contact their physician right away if they experience, depression, anxiety, or signs of psychosis or mania.

Pregnancy
Advise women that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUVIGIL during pregnancy [see Use in Specific Populations (8.11)].

Females of Reproductive Potential
Caution females regarding the potential increased risk of pregnancy when using hormonal contraceptives (including depot or implantable contraceptives) with NUVIGIL and advise females who are using a hormonal method of contraception to use an additional barrier method or an alternative non-hormonal method of contraception during treatment with NUVIGIL and for one month after discontinuation of NUVIGIL.

Concomitant Medication
Advise patients to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, because of the potential for interactions between NUVIGIL and other drugs.

Alcohol
Advise patients that the use of NUVIGIL in combination with alcohol has not been studied. Advise patients that it is prudent to avoid alcohol while taking NUVIGIL.

NUV-009
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North Wales, PA 19454
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• Your doctor will tell you the right time of day to take NUVIGIL.
  ◦ People with narcolepsy or OSA usually take NUVIGIL one time
each day in the morning.
  ◦ People with SWD usually take NUVIGIL about 1 hour before
their work shift.
• Do not change the time of day you take NUVIGIL unless you
have talked to your doctor. If you take NUVIGIL too close to your
bedtime, you may find it harder to go to sleep.
• You can take NUVIGIL with or without food.
• If you take more than your prescribed dose or if you take an
overdose of NUVIGIL, call your doctor or poison control center
right away.

Symptoms of an overdose of NUVIGIL may include:
• Trouble sleeping
• Confusion
• Feeling excited
• Nausea and diarrhea
• Chest pain
• Anxiety
• Restlessness
• Feeling disoriented
• Hearing, seeing, feeling, or sensing things that are not really
there (hallucinations)
• A fast or slow heartbeat
• Increased blood pressure
• Shortness of breath

What should I avoid while taking NUVIGIL?
• Do not drive a car or do other dangerous activities until you know
how NUVIGIL affects you. People with sleep disorders should
always be careful about doing things that could be dangerous.
Do not change your daily habits until your doctor tells you it is
okay.
• You should avoid drinking alcohol. It is not known how drinking
alcohol will affect you when taking NUVIGIL.

What are the possible side effects of NUVIGIL?
NUVIGIL may cause serious side effects. Stop taking NUVIGIL
and call your doctor right away or get emergency help if you get
any of the following:
• a serious rash or serious allergic reaction. (See “What is the
most important information I should know about NUVIGIL?”)
• mental (psychiatric) symptoms, including:
  ◦ depression
  ◦ hearing, seeing, feeling, or sensing things that are not really
there (hallucinations)
  ◦ thoughts of suicide
  ◦ other mental problems
  ◦ feeling anxious
  ◦ an extreme increase in activity and talking (mania)
  ◦ aggressive behavior
• symptoms of a heart problem, including chest pain, abnormal
heart beats, and trouble breathing.
The most common side effects of NUVIGIL include:
• headache
• dizziness
• nausea
• trouble sleeping
These are not all the possible side effects of NUVIGIL.
Call your doctor for medical advice about side effects. You may
report side effects to FDA at 1-800-FDA-1088.

How should I store NUVIGIL?
• Store NUVIGIL at room temperature between 68° to 77°F (20° to
25°C).
• Keep NUVIGIL and all medicines out of the reach of children.