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

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, dizziness, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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Postmarketing adverse reactions associated with the use of NUVIGIL, some of which have resulted in hospitalization, have included mania, delusions, hallucinations, suicidal ideation, and aggression. Many, but not all, patients who developed psychiatric adverse reactions had a prior psychiatric history. In these cases, reported NUVIGIL total daily doses ranged from 50 mg to 450 mg, which includes doses below and above the recommended dosages.

5.6 Effects on Ability to Drive and Use Machinery

Although NUVIGIL has not been shown to produce functional impairment, any drug affecting the central nervous system (CNS) may alter judgment, thinking or motor skills. Patients should be cautioned about operating an automobile or other hazardous machinery until it is reasonably certain that NUVIGIL therapy will not adversely affect their ability to engage in such activities.

5.7 Cardiovascular Events

In clinical studies of modafinil, cardiovascular adverse reactions, including chest pain, palpitations, dyspnea and transient ischemic T-wave changes on ECG were observed in three subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that 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 mmHg and 0.9 mmHg, respectively). This rise did not differ in 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 is recommended when NUVIGIL is used in 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)]

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

<table>
<thead>
<tr>
<th>NUVIGIL® (%) N=645</th>
<th>Placebo (%) N=445</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>1 %</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 %</td>
</tr>
<tr>
<td>Contact Dermatitis</td>
<td>1 %</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>1 %</td>
</tr>
<tr>
<td>Depressed Mood</td>
<td>1 %</td>
</tr>
<tr>
<td>Disturbance In Attention</td>
<td>1 %</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 %</td>
</tr>
<tr>
<td>Hyperhydrosis</td>
<td>1 %</td>
</tr>
<tr>
<td>Increased Gamma-Glutamyltransferase</td>
<td>1 %</td>
</tr>
<tr>
<td>Increased Heart Rate</td>
<td>1 %</td>
</tr>
<tr>
<td>Influenza-Like Illness</td>
<td>1 %</td>
</tr>
<tr>
<td>Loose Stools</td>
<td>1 %</td>
</tr>
<tr>
<td>Migraine</td>
<td>1 %</td>
</tr>
<tr>
<td>Nervousness</td>
<td>1 %</td>
</tr>
<tr>
<td>Pain</td>
<td>1 %</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1 %</td>
</tr>
<tr>
<td>Polyuria</td>
<td>1 %</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 %</td>
</tr>
<tr>
<td>Seasonal Allergy</td>
<td>1 %</td>
</tr>
<tr>
<td>Thirst</td>
<td>1 × 10⁻³</td>
</tr>
<tr>
<td>Tremor</td>
<td>1 %</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 %</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 (%) N=138</th>
<th>NUVIGIL® 150 mg (%) N=447</th>
<th>NUVIGIL® Combined (%) N=645</th>
<th>Placebo (%) N=445</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>23 %</td>
<td>14 %</td>
<td>17 %</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 %</td>
<td>6 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 %</td>
<td>4 %</td>
<td>5 %</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>7 %</td>
<td>2 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Rash</td>
<td>4 %</td>
<td>1 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Depression</td>
<td>3 %</td>
<td>1 %</td>
<td>2 %</td>
</tr>
</tbody>
</table>

Adverse Reactions Resulting in Discontinuation of Treatment

In placebo-controlled clinical trials, 44 of the 645 patients (7%) who received NUVIGIL discontinued due to an adverse reaction compared to 16 of the 445 (4%) of patients that received placebo. The most frequent reason for discontinuation was headache (1%).

Laboratory Abnormalities

Clinical chemistry, hematology, and urinalysis parameters were monitored in the studies. Mean plasma levels of gamma glutamyltransferase (GGT) and alkaline phosphatase (AP) were found to be higher following administration of NUVIGIL, but were not placebo. Few patients, however, had GGT or AP elevations outside of the normal range. No differences were apparent in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, or total bilirubin, although there were rare cases of isolated elevations of AST and/or ALT. A single case of mild pancytopenia was observed after 35 days of treatment and resolved with drug discontinuation. A small mean decrease from baseline in serum uric acid compared to placebo was seen in clinical trials. The clinical significance of this finding is unknown.

6.2 Postmarketing Experience

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.

Cardiovascular: Stroke

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

7 DRUG INTERACTIONS

Effects of NUVIGIL on CYP3A4/5 Substrates

The clearance of drugs that are substrates for CYP3A4/5 (e.g., steroidal contraceptives, cyclosporine, midazolam, and triazolam) may be increased by NUVIGIL via induction of metabolic enzymes, which results in lower systemic exposure. Dosage adjustment of these drugs should be considered when these drugs are used concomitantly with NUVIGIL [see Clinical Pharmacology (12.3)].

The effectiveness of steroidal contraceptives may be reduced when used with NUVIGIL and for one month after discontinuation of therapy. Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptives (e.g., ethinyl estradiol) when treated concomitantly with NUVIGIL and for one month after discontinuation of NUVIGIL treatment.

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 is 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 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 abortion.

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 resulted in decreased fetal weight and increased incidences 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 highest no-effect dose for embryofetal developmental toxicity in rat (200 mg/kg/day) was associated with plasma modafinil exposure (AUC) less than that in humans at the MRHD of NUVIGIL. 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 modafinil 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. NUVIGIL 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.

Risk Summary

There is 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. Armodafinil was present in rat milk when animals were dosed during the lactation period. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for armodafinil and any potential adverse effects on the breastfed child from armodafinil or from the underlying maternal condition.
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)].

8.4 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 in NUvigil, poses a risk of overdose similar to that seen for modafinil, which may lead to tachycardia, insomnia, agitation, dizziness, anxiety, nausea, headache, dystonia, tremor, chest pain, hypertension, seizures, hypothyroidism, and hyperglycemia. Other signs and symptoms of CNS side effects of misuse include tachypnea, sweating, dilated pupils, hyperactivity, restlessness, decreased appetite, 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 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 has been observed in a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs 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 ataxia. Drug withdrawal convulsions, suicidality, fatigue, insomnia, aches, depression and headache have also been observed during the postmarketing period. Also, abrupt withdrawal can have 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 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. Armofinil is the R- enantiomer of modafinil which is a 1.1 times more potent on the R- and S-enantiomers. The chemical name for armodafinil is 2-[(R)-(diphenylmethyl)sulfanyl] acetamide. The molecular formula is C21H21NO3S and the molecular weight is 272.35.

Armodafinil is a white to off-white, crystalline powder that is slightly soluble in water, sparingly soluble in acetone, and soluble in methanol.

NUvigil tablets contain 50, 150, 200 or 250 mg of armodafinil and the following inactive ingredients: croscarmellose sodium, 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. Armofinil (R-modafinil) has pharmacological properties similar to those of some of the non-selective central nervous system (CNS) stimulants. Armofinil has been shown to improve alertness in patients with narcolepsy in studies. The R- and S-enantiomers have similar pharmacological actions in animals. Armofinil and modafinil have wake-promoting actions similar to sympathomimetic agents including amphetamine and methylphenidate, although their pharmacologic properties are not identical to that of the sympathomimetic amines. Modafinil-induced wakefulness can be attenuated by the a1-adrenergic receptor antagonist, prazosin; however, modafinil is inactive in other in vitro assay systems known to be responsive to a1-adrenergic agonists such as the rat vas deferens preparation.

Modafinil 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 levels in some brain regions of animals. In genetically engineered mice lacking the dopamine transporter (DAT), modafinil lacked wake-promoting activity, suggesting that this activity was DAT-dependent. However, the wake-promoting effects of modafinil, unlike those of amphetamine, were not antagonized by the dopamine receptor antagonist haloperidol in rats. In addition, alpha-methyl-p-tyrosine, a dopamine synthesis inhibitor, blocks the action of amphetamine, but does not block locomotor activity induced by modafinil.

In addition to its wake-promoting effects and ability to increase locomotor activity in animals, modafinil produces psychostimulant-like and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants in humans. Modafinil has reinforcing properties, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine; 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.

12.2 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 pharmacokinetic exposure for armodafinil is 1.8 times the exposure observed following 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 of R- and S-enantiomers) are nearly superimposable. However, the Cmax and AUC0-∞ of armodafinil at 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.

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. Food effect on the overall bioavailability of NUvigil is considered 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.

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 interactions of NUvigil with highly protein-bound drugs is considered to be minimal.

Elimination
After oral administration of NUvigil, armodafinil exhibits an apparent nonexponential decline from the peak plasma concentration. The apparent terminal t1/2 is approximately 15 hours. The oral clearance of NUvigil is approximately 33 ml/min.

Metabolism
In vitro and in vivo data show that armodafinil 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 next in importance.
 NUVIDIL® (armodafinil) tablets, for oral use, C-IV

- **Interactions with CNS Active Drugs**
  Concomitant administration of NUVIDIL with quetiapine reduced the systemic exposure of quetiapine.
  Data specific to NUVIDIL drug-drug interaction potential with other CNS active drugs are not available. However, the following available drug-drug interaction information on modafinil should be applicable to NUVIDIL.
  Concomitant administration of modafinil with monoamine oxidase (MAO) inhibitors 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 NUVIDIL or modafinil drug-drug interaction potential with monoamine oxidase (MAO) inhibitors are not available [see Drug Interactions (7)].

- **Interactions with P-Glycoprotein**
  An in vitro study demonstrated that armodafinil is a substrate of P-glycoprotein.
  The impact of inhibition of P-glycoprotein is not known.

- **Interactions with Other Drugs**
  Data specific to NUVIDIL drug-drug interaction potential for additional other drugs are not available. However, the following available drug-drug interaction information on modafinil should be applicable to NUVIDIL.
  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)].

### Nonclinical Toxicology

#### 13 Carcinogenesis, Mutagenesis, Impairment of Fertility

- **Carcinogenesis**
  In a mouse carcinogenicity study, modafinil (R-modafinil) was administered at oral doses 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-warfarin) 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 modafinil exposures (AUC) were less than that in humans at the MRHD of NUVIDIL (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.

- **Impairment of Fertility**
  Armodafinil 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 embryocell) or in vivo (mouse bone marrow micronucleus) assays.

### Clinical Studies

#### 14.1 Obstructive Sleep Apnea (OSA)

The effectiveness of NUVIDIL in improving wakefulness in patients with excessive sleepiness associated with OSA was established in two 12-week, multi-center, 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 general, or associated 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 of up to 400 mg/day were included with up to 300 mg/day in males and 100 mg/day in females. 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
NUVIGIL® (armodafinil) tablets, for oral use, C-IV

without using extraordinary measures. Each test session was terminated after 20 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 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 at scale final visit (Table 4). A statistically significant greater number of patients treated with NUVIGIL showed improvement in overall clinical condition as rated by the CGI-C at scale final visit (Table 4).

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]. Patients treated with NUVIGIL showed a statistically significant prolongation in the time to sleep onset compared to placebo-treated patients, as measured by the nighttime sleep latency. A statistically significant greater number of patients treated with NUVIGIL showed improvement in overall clinical condition as rated by the CGI-C at scale final visit (Table 4). Daytime sleep measured with polysomnography was not affected by the use of NUVIGIL.

### 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 include: 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, disrupted sleep, and other sleep-related problems. In this study, 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, was performed on an unstimulating environment, measured latency (in minutes) to sleep onset averaged over 4 test sessions at 2-hour 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 improvement 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 magnitudes 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 met the criteria for chronic SWD. The criteria include: 1) either, a) 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 or 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 nights 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.

#### Table 3: Average Baseline Sleep Latency and Change from Baseline at Final Visit (MWT and MSLT in minutes)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Measure</th>
<th>NUVIGIL 150 mg*</th>
<th>NUVIGIL 250 mg*</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change from Baseline</td>
<td>Baseline</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td>OSA I</td>
<td>MWT</td>
<td>21.5</td>
<td>1.7</td>
<td>23.3</td>
</tr>
<tr>
<td>OSA II</td>
<td>MWT</td>
<td>23.7</td>
<td>2.3</td>
<td>-</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>MWT</td>
<td>12.1</td>
<td>1.3</td>
<td>9.5</td>
</tr>
<tr>
<td>SWD</td>
<td>MSLT</td>
<td>2.3</td>
<td>3.1</td>
<td>-</td>
</tr>
</tbody>
</table>

*Significantly different than placebo for all trials (p<0.05)

#### Table 4: Clinical Global Impression of Change (CGI-C) (Percent of Patients Who Improved at Final Visit)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>NUVIGIL 150 mg*</th>
<th>NUVIGIL 250 mg*</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA I</td>
<td>71%</td>
<td>74%</td>
<td>34%</td>
</tr>
<tr>
<td>OSA II</td>
<td>71%</td>
<td>-</td>
<td>53%</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>69%</td>
<td>73%</td>
<td>33%</td>
</tr>
<tr>
<td>SWD</td>
<td>79%</td>
<td>-</td>
<td>59%</td>
</tr>
</tbody>
</table>

*Significantly different than placebo for all trials (p<0.05)

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

NUVIGIL® (armodafinil) Tablets are available as follows:

- **50 mg**: Each round, white to off-white tablet is debossed with “250” on one side and “225” on the other.
- **150 mg**: Each round, white to off-white tablet is debossed with “250” on one side and “225” on the other.
- **200 mg**: Each round, white to off-white tablet is debossed with “250” on one side and “225” on the other.
- **250 mg**: Each oval, white to off-white tablet is debossed with “250” on one side and “225” on the other.

#### 16.2 Storage

Store at 20° to 25°C (68° to 77°F).

### 17 PATIENT COUNSELING INFORMATION

Advis patients and caregivers about the risk of potentially fatal serious skin reactions. Educate patients about the signs and symptoms that may signal a serious skin reaction. Instruct patients to discontinue NUVIGIL and consult with their healthcare provider immediately if a skin reaction such as rash, mouth sores, blisters, or peeling skin occurs during treatment with NUVIGIL [see Warnings and Precautions (5.1)].

#### Drug/Multi-organ Hypersensitivity

Instruct patients that a fever associated with signs of other organ system involvement (e.g., rash, lymphadenopathy, hepatic dysfunction) may be drug-related and should be reported to their healthcare provider immediately [see Warnings and Precautions (5.2)].

#### Angioedema and Anaphylactic Reactions

Advis patients of life-threatening symptoms suggesting anaphylaxis or angioedema (such as hives, difficulty in swallowing or breathing, hoarseness, or swelling of the face, eyes, lips, or tongue) that can occur with NUVIGIL. Instruct them to discontinue NUVIGIL and immediately report these symptoms to their healthcare provider [see Warnings and Precautions (5.3)].

#### Wakefulness

Advis patients that treatment with NUVIGIL will not eliminate their abnormal tendency to fall asleep.
NUVIGIL® (armodafinil) tablets, for oral use, C-IV

Continuing Previously Prescribed Treatments
Inform patients that it may be critical that they continue to take their previously prescribed treatments (e.g., patients with OSA receiving CPAP should continue to do so).

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 (8.1)].

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-010
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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
• obstructive sleep apnea (OSA). NUVIGIL is used with other medical treatments for this sleep disorder. NUVIGIL does not take the place of using your CPAP machine or other treatments that your doctor has prescribed for this condition. It is important that you continue to use these treatments as prescribed by your doctor.
• shift work disorder (SWD)
NUVIGIL will not cure these sleep disorders. NUVIGIL may help the sleepiness caused by these conditions, but it may not stop all your sleepiness. NUVIGIL does not take the place of getting enough sleep. Follow your doctor’s advice about good sleep habits and using other treatments.

Do not take NUVIGIL:
• are allergic to any of its ingredients. See the end of this Medication Guide for a complete list of ingredients in NUVIGIL.
• have had a rash or allergic reaction to either armodafinil (NUVIGIL) or modafinil (PROVIGIL®). These medicines are very similar.

Before you take NUVIGIL, tell your doctor about all of your medical conditions, including if you:
• have a history of mental health problems, including psychosis
• have heart problems or had a heart attack
• have high blood pressure. Your blood pressure may need to be checked more often while taking NUVIGIL.
• have liver or kidney problems
• have a history of drug or alcohol abuse or addiction
• are pregnant or planning to become pregnant. It is not known if NUVIGIL will harm your unborn baby.

Pregnancy Registry: There is a registry for women who become pregnant during treatment with NUVIGIL. The purpose of this registry is to collect information about the safety of NUVIGIL during pregnancy. Contact the registry as soon as you learn that you are pregnant, or ask your doctor to contact the registry for you. You or your doctor can get information and enroll you in the registry by calling 1-866-404-4106.
• are breastfeeding. It is not known if NUVIGIL passes into your milk. Talk to your doctor about the best way to feed your baby if you take NUVIGIL.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. NUVIGIL and many other medicines can interact with each other, sometimes causing side effects. NUVIGIL may affect the way other medicines work, and other medicines may affect how NUVIGIL works. Your dose of NUVIGIL or certain other medicines may need to be changed.
Especially, tell your doctor if you use or take:
• a hormonal birth control method, such as birth control pills, shots, implants, patches, vaginal rings, and intrauterine devices (IUDs). Hormonal birth control methods may not work while you take NUVIGIL. Women who use one of these methods of birth control may have a higher chance for getting pregnant while taking NUVIGIL, and for 1 month after stopping NUVIGIL. You should use effective birth control while taking NUVIGIL and for 1 month after your final dose. Talk to your doctor about birth control choices that are right for you while taking NUVIGIL.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine. Your doctor or pharmacist will tell you if it is safe to take NUVIGIL and other medicines together. Do not start any new medicines with NUVIGIL unless your doctor has told you it is okay.
### How should I take NUVIGIL?
- Take NUVIGIL exactly as prescribed by your doctor. Your doctor will prescribe the dose of NUVIGIL that is right for you. Do not change your dose of NUVIGIL without talking to your doctor.
- 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.