APOTEX

PRINTED PACKAGING MATERIAL MASTER

New Material Code: 040-T-00725	ECL Common Text#: N/A	Description: 1225033 Armodafinil Tablets Outsert-Patient Leaflet United States
SAP Ref #: 71802, 71804, 71805, 71806 (ZERT)		
Old Material Code: 040-T-00725	C of A: N/A	Change Control #: 1712960
Pantone Colours: BLACK		DIELINE
Dimensions/Dieline#: Thirdparty (Aphena Pharma Solutions) Flat: 825.5 x 304.8 mm (32.5" x 12") - Folded: 31.75 x 63.5 mm (1.25" x 2.5")	Minimum Font Size: 6 pt	Version No. 2 Cycle No.: 1

If applicable, 2D code will be added to the artwork by the vendor at the time of printing and will be unique to each topsert.
NOTE: Pharmacode is vendor specific information and may vary

63.5 mm (2.5")

825.5 mm (32.5")

156.4 mm (6.1562")

304.8 mm (12")

101.6 mm (4")

32.5 mm (1.28")

35.7 mm (1.375")

GLUE AREA

040-T-00725

NUVIGIL® (armodafinil) Tablets CIV

Medication Guide Required: Each time NUVIGIL is dispended, give the patient a Medication Guide.

℞ Only Revised: 02/2025

040-T-00725

NUVIGIL® (armodafinil) Tablets CIV

Medication Guide Required: Each time NUVIGIL is dispended, give the patient a Medication Guide.

℞ Only Revised: 02/2025

GLUE AREA

TEXT NEEDS TO BE PLACED APPROX. A MINIMUM OF 1/8" = 3.2mm FROM OUTSIDE EDGES

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NUVIGIL safely and effectively. See full prescribing information for NUVIGIL.

NUVIGIL® (armodafinil) tablets, for oral use, C-IV
Initial U.S. Approval: 2007

------------------------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.

--------------------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 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)

------------------DOSAGE FORMS AND STRENGTHS------------------

Tablets: 50 mg, 150 mg, 200 mg, and 250 mg. (3)

-------------------------CONTRAINDICATIONS-------------------------

NUVIGIL is contraindicated in patients with known hypersensitivity to modafinil or armodafinil. (4)

--------------------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, nausea, dizziness, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-706-5575 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.

Revised: 02/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

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).

Limitations of Use
In OSA, NUVIGIL is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating NUVIGIL for excessive sleepiness.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Obstructive Sleep Apnea (OSA) and Narcolepsy

The recommended dosage of NUVIGIL for patients with OSA or narcolepsy is 150 mg to 250 mg taken orally once a day as a single dose in the morning.

In patients with OSA, doses up to 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that these doses confer additional benefit beyond that of the 150 mg/day dose *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1, 14.2)]*.

2.2 Dosage in Shift Work Disorder (SWD)

The recommended dosage of NUVIGIL for patients with SWD is 150 mg taken orally once a day as a single dose approximately 1 hour prior to the start of their work shift.

2.3 Dosage Modification in Patients with Severe Hepatic Impairment

In patients with severe hepatic impairment, the dosage of NUVIGIL should be reduced *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.4 Use in Geriatric Patients

Consideration should be given to the use of lower doses and close monitoring in geriatric patients *[see Use in Specific Populations (8.5)]*.

3 DOSAGE FORMS AND STRENGTHS

- 50 mg – round, white to off-white tablet with C on one side and "205" on the other
- 150 mg – oval, white to off-white tablet with C on one side and "215" on the other
- 200 mg – rounded, rectangular, white to off-white tablet with C on one side and "220" on the other
- 250 mg – oval, white to off-white tablet with C on one side and "225" on the other

4 CONTRAINDICATIONS

NUVIGIL is contraindicated in patients with known hypersensitivity to modafinil or armodafinil or its inactive ingredients *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Dermatologic Reactions, including Stevens-Johnson Syndrome and Toxic Epidermal Necrosis

Serious rash requiring hospitalization and discontinuation of treatment has been reported in association with the use of NUVIGIL (armodafinil) or modafinil (the racemic mixture of S- and R-enantiomers).

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 postmarketing 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 postmarketing experience 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 with symptoms beginning after prolonged treatment (e.g., 3 months).

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 System Symptoms (DRESS)/Multiorgan Hypersensitivity

DRESS, also known as multi-organ hypersensitivity, has been reported with NUVIGIL. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, 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 though 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. Although there are no case reports to indicate cross-sensitivity with other drugs that produce this syndrome, the experience with drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

5.3 Angioedema and Anaphylaxis Reactions

Angioedema and hypersensitivity (with rash, dysphagia, and bronchospasm), were observed with NUVIGIL. Patients should be advised to discontinue therapy and immediately report to their physician any signs or symptoms suggesting angioedema or anaphylaxis (e.g., swelling of face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness).

5.4 Persistent Sleepiness

Patients with abnormal levels of sleepiness who take NUVIGIL should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking NUVIGIL, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

5.5 Psychiatric Symptoms

In pre-approval narcolepsy, OSA and SWD controlled trials of NUVIGIL, anxiety, agitation, nervousness, and irritability were reasons for treatment discontinuation more often in patients on NUVIGIL compared to placebo (NUVIGIL 1.2% and placebo 0.3%). Depression was also a reason for treatment discontinuation more often in patients on NUVIGIL compared to placebo (NUVIGIL 0.6% and placebo 0.2%). Cases of suicidal ideation were observed in clinical trials. Caution should be exercised when NUVIGIL is given to patients with a history of psychosis, depression, or mania. If psychiatric symptoms develop in association with NUVIGIL administration, consider discontinuing NUVIGIL.

Psychiatric adverse reactions have been reported in patients treated with modafinil. Modafinil and NUVIGIL (armodafinil) are very closely related. Therefore, the incidence and type of psychiatric symptoms associated with NUVIGIL are expected to be similar to the incidence and type of these events with modafinil.

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 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 when 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 System Symptoms (DRESS)/Multiorgan 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)

	NUVIGIL (%) N=645	Placebo (%) N=445
Headache	17	9
Nausea	7	3
Dizziness	5	2
Insomnia	5	1
Anxiety	4	1
Diarrhea	4	2
Dry Mouth	4	1
Depression	2	0
Dyspepsia	2	0
Fatigue	2	1
Palpitations	2	1
Rash	2	0
Upper Abdominal Pain	2	1
Agitation	1	0
Anorexia	1	0
Constipation	1	0
Contact Dermatitis	1	0
Decreased Appetite	1	0
Depressed Mood	1	0
Disturbance In Attention	1	0
Dyspnea	1	0
Hyperhydrosis	1	0
Increased Gamma-Glutamyltransferase	1	0
Increased Heart Rate	1	0
Influenza-Like Illness	1	0
Loose Stools	1	0
Migraine	1	0
Nervousness	1	0
Pain	1	0
Paresthesia	1	0
Polyuria	1	0
Pyrexia	1	0
Seasonal Allergy	1	0
Thirst	1	0
Tremor	1	0
Vomiting	1	0

* 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

	NUVIGIL 250 mg (%) N=198	NUVIGIL 150 mg (%) N=447	NUVIGIL Combined (%) N=645	Placebo (%) N=445
Headache	23	14	17	9
Nausea	9	6	7	3
Insomnia	6	4	5	1
Dry Mouth	7	2	4	<1
Rash	4	1	2	<1
Depression	3	1	2	<1

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 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.

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 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 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 resulted in decreased fetal body 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 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. Modafinil 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 of NUVIGIL, poses a risk of overdosage similar to that seen for modafinil, which may lead to tachycardia, insomnia, agitation, dizziness, anxiety, nausea, headache, dystonia, tremor, chest pain, hypertension, seizures, delirium, or hallucinations. Other signs and symptoms of CNS stimulant abuse 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 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.

MEDICATION GUIDE
NUVIGIL (nu-vij-el) CIV
(armodafinil)
tablets, for oral use,

Medication Guide available at
https://www.apotex.com/products/us/mg.asp

Read this Medication Guide before you start taking NUVIGIL and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

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
- 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.
  - o People with narcolepsy or OSA usually take NUVIGIL one time each day in the morning.
  - o 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:**
  - o depression
  - o hearing, seeing, feeling, or sensing things that are not really there (hallucinations)
  - o thoughts of suicide
  - o other mental problems
  - o feeling anxious
  - o an extreme increase in activity and talking (mania)
  - o aggressive behavior
- **symptoms of a heart problem**, including chest pain, abnormal heart beats, and trouble breathing.

MEDICATION GUIDE
NUVIGIL (nu-vij-el) CIV
(armodafinil)
tablets, for oral use,

Medication Guide available at
https://www.apotex.com/products/us/mg.asp

Read this Medication Guide before you start taking NUVIGIL and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

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
- 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.
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  - o depression
  - o hearing, seeing, feeling, or sensing things that are not really there (hallucinations)
  - o thoughts of suicide
  - o other mental problems
  - o feeling anxious
  - o an extreme increase in activity and talking (mania)
  - o aggressive behavior
- **symptoms of a heart problem**, including chest pain, abnormal heart beats, and trouble breathing.

APOTEX

PRINTED PACKAGING MATERIAL MASTER

New Material Code: 040-T-00725	ECL Common Text#: N/A	Description: 1225033 Armodafinil Tablets Outsert-Patient Leaflet United States
SAP Ref #: 71802, 71804, 71805, 71806 (ZERT)		

If applicable, 2D code will be added to the artwork by the vendor at the time of printing and will be unique to each topsert.
NOTE: Pharmacode is vendor specific information and may vary

825.5 mm (32.5")

304.8 mm (12")

The most common side effects of NUVIGIL include:
- headache
- nausea
- dizziness
- 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°F to 77°F (20°C to 25°C).
- **Keep NUVIGIL and all medicines out of the reach of children.**

General information about the safe and effective use of NUVIGIL.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NUVIGIL for a condition for which it was not prescribed. Do not give NUVIGIL to other people, even if they have the same symptoms that you have. It may harm them and is against the law.
You can ask your pharmacist or healthcare provider for information about NUVIGIL that is written for health professionals.

What are the ingredients in NUVIGIL?
Active ingredient: armodafinil
Inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, povidone, and magnesium stearate.

Manufactured for:
Apotex Corp.
Weston, Florida
33326 USA

ApoPharma is a registered trademark of Apotex Inc

For more information, go to www.apotex.com or call 1-800-706-5575.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: February 2025

The most common side effects of NUVIGIL include:
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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 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 atrial fibrillation.

Drug withdrawal convulsions, suicidality, fatigue, insomnia, aches, depression and headache have also been observed during the postmarketing period. Also, abrupt 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).

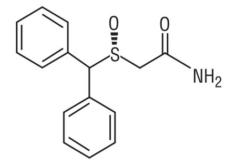
Multiple cases of development of tolerance to NUVIGIL have been reported during the postmarketing period.

10 OVERDOSAGE
Fatal overdoses involving modafinil alone or involving NUVIGIL or modafinil 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)- (diphenylmethyl)sulfinyl]acetamide. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.35.

The chemical structure is:



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, 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 α-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 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 psychoactive 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.

12.3 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 of R- and S-enantiomers) are nearly superimposable. However, the C_{max} and $AUC_{0-\infty}$, 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 (t_{max}) may be delayed by approximately 2-4 hours in the fed state. Since the delay in t_{max} 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 monoexponential decline from the peak plasma concentration. The apparent terminal $t_{½}$ 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 deamidation, 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. 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).

Specific Populations
Age
In a clinical study, systemic exposure of armodafinil was approximately 15% higher in elderly subjects (≥65 years of age, N=24), corresponding to approximately 12% lower oral clearance (CL/F), as compared to young subjects (18-45 years of age, N=25). Systemic exposure of armodafinil acid (metabolite) was approximately 61% and 73% greater for C_{max} and $AUC_{0-\tau}$, respectively, compared to young subjects. Systemic exposure of the sulfone metabolite was approximately 20% lower for elderly subjects compared with young subjects. A subgroup analysis of elderly subjects demonstrated elderly subjects ≥75 and 65-74 years of age had approximately 21% and 9% lower oral clearance, respectively, compared to young subjects. Systemic exposure was approximately 10% greater in subjects 65-74 years of age (N=17) and 27% greater in subjects ≥75 years of age (N=7), respectively, when compared to young subjects. The change is considered not likely to be clinically significant for elderly patients, however, because some elderly patients have greater exposure to armodafinil, consideration should be given to the use of lower doses.

Sex
Population pharmacokinetic analysis suggests no gender effect on the pharmacokinetics of armodafinil.

Ethnicity
The influence of race/ethnicity on the pharmacokinetics of armodafinil has not been studied.

Hepatic Impairment
The pharmacokinetics and metabolism of modafinil were examined in patients with cirrhosis of the liver (6 men and 3 women). Three patients had stage B or B+ cirrhosis and 6 patients had stage C or C+ cirrhosis (per the Child-Pugh score criteria). Clinically 8 of 9 patients were icteric and all had ascites. In these patients, the oral clearance of modafinil was decreased by about 60% and the steady state concentration was doubled compared to normal patients *[see Dosage and Administration (2.3) and Use in Specific Populations (8.6)]*.

Renal Impairment
In a single dose 200 mg modafinil study, severe chronic renal failure (creatinine clearance ≤20 mL/min) did not significantly influence the pharmacokinetics of modafinil, but exposure to modafinil acid (metabolite) was increased 9-fold.

Drug Interactions
In vitro data demonstrated that armodafinil weakly induces CYP1A2 and possibly CYP3A activities in a concentration-related manner and that CYP2C19 activity is reversibly inhibited by armodafinil. Other CYP activities did not appear to be affected by armodafinil. An in vitro study demonstrated that armodafinil is a substrate of P-glycoprotein.

Potential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Cytochrome P450 Isoenzymes and Other Hepatic Enzymes

The existence of multiple pathways for armodafinil metabolism, as well as the fact that a non-CYP-related pathway is the most rapid in metabolizing armodafinil, suggest that there is a low probability of substantive effects on the overall pharmacokinetic profile of NUVIGIL due to CYP inhibition by concomitant medications. However, due to the partial involvement of CYP3A enzymes in the metabolic elimination of armodafinil, coadministration of potent inducers of CYP3A4/5 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4/5 (e.g., ketoconazole, erythromycin) could alter the plasma concentrations of armodafinil.

The Potential of NUVIGIL to Alter the Metabolism of Other Drugs by Enzyme Induction or Inhibition
- Drugs Metabolized by CYP3A4/5
  In vitro data demonstrated that armodafinil is a weak inducer of CYP3A activity in a concentration-related manner. In a clinical study, concomitant administration of NUVIGIL 250 mg resulted in a reduction in systemic exposure to midazolam by 32% after a single oral dose (5 mg) and 17% after a single intravenous dose (2 mg). Therefore, the blood levels and effectiveness of drugs that are substrates for CYP3A enzymes (e.g., steroidal contraceptives, cyclosporine, midazolam, and triazolam) may be reduced after initiation of concomitant treatment with NUVIGIL *[see Drug Interactions (7)]*.

  In a separate clinical study, concomitant administration of NUVIGIL 250 mg with quetiapine (300 mg to 600 mg daily doses) resulted in a reduction in the mean systemic exposure of quetiapine by approximately 29%. No dose adjustment is required.
- Drugs Metabolized by CYP1A2
  In vitro data demonstrated that armodafinil is a weak inducer of CYP1A2 in a concentration-related manner. However, in a clinical study using caffeine as a probe substrate, no significant effect on CYP1A2 activity was observed.
- Drugs Metabolized by CYP2C19
  In vitro data demonstrated that armodafinil is a reversible inhibitor of CYP2C19 activity. In a clinical study, concomitant administration of NUVIGIL 400 mg resulted in a 40% increase in exposure to omeprazole after a single oral dose (40 mg), as a result of moderate inhibition of CYP2C19 activity *[see Drug Interactions (7)]*.
- Interactions with CNS Active Drugs
  Concomitant administration of NUVIGIL with quetiapine reduced the systemic exposure of quetiapine.

  Data specific to NUVIGIL 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 NUVIGIL.

  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
  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 NUVIGIL 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 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 armodafinil 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 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, bradytachycardia, 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 latencies (in minutes) in the MWT at baseline for the trials are shown in Table 3 below, along with the average change from baseline on the MWT at final visit. The percentages of patients who showed any degree of improvement on the CGI-C in the clinical trials are shown in Table 4 below. The two doses of NUVIGIL produced statistically significant effects of similar magnitudes on the MWT, and also on the CGI-C.

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 include either: 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 major sleep episode; and polysomnography 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. For entry 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 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 on the MWT at each dose 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 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*]*.

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 MSLT at final visit (*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 at final visit (*Table 4*).

Daytime sleep measured with polysomnography was not affected by the use of NUVIGIL.

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

Disorder	Measure	NUVIGIL 150 mg*		NUVIGIL 250 mg*		Placebo	
		Baseline	Change from Baseline	Baseline	Change from Baseline	Baseline	Change from Baseline
OSA I	MWT	21.5	1.7	23.3	2.2	23.2	-1.7
OSA II	MWT	23.7	2.3	-	-	23.3	-1.3
Narcolepsy	MWT	12.1	1.3	9.5	2.6	12.5	-1.9
SWD	MSLT	2.3	3.1	-	-	2.4	0.4

*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)

Disorder	NUVIGIL 150 mg*	NUVIGIL 250 mg*	Placebo
OSA I	71%	74%	37%
OSA II	71%	-	53%
Narcolepsy	69%	73%	33%
SWD	79%	-	59%

*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 on one side and "205" on the other. NDC 60505-4846-3 – Bottles of 30
- 150 mg: Each oval, white to off-white tablet is debossed with on one side and "215" on the other. NDC 60505-4847-3 – Bottles of 30
- 200 mg: Each rounded, rectangular, white to off-white tablet is debossed with on one side and "220" on the other. NDC 60505-4849-3 – Bottles of 30
- 250 mg: Each oval, white to off-white tablet is debossed with on one side and "225" on the other. NDC 60505-4850-3 – Bottles of 30

16.2 Storage
Store at 20° C - 25° C (68° F - 77° F).

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Serious Dermatologic Reactions
Advise 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)]*.

DRESS/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
Advise 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
Advise patients that treatment with NUVIGIL will not eliminate their abnormal tendency to fall asleep. Advise patients that they should not alter their previous behavior with regard to potentially dangerous activities (e.g., driving, operating machinery) or other activities requiring appropriate levels of wakefulness, until and unless treatment with NUVIGIL has been shown to produce levels of wakefulness that permit such activities. Advise patients that NUVIGIL is not a replacement for sleep.

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.

Dispense with Medication Guide available at https://www.apotex.com/products/us/mg.asp

Manufactured for:
Apotex Corp.
Weston, Florida
33326 USA

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TEXT NEEDS TO BE PLACED APPROX.
A MINIMUM OF 1/8" = 3.2mm
FROM OUTSIDE EDGES