

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-875

LABELING

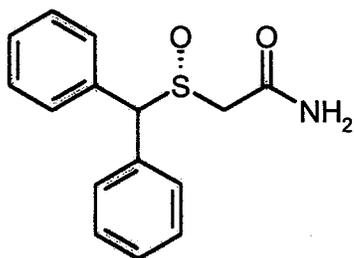
1 **NUVIGIL™ (armodafinil) Tablets [C-IV]**

Rx Only

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4
5 **DESCRIPTION**

6 NUVIGIL™ (armodafinil) is a wakefulness-promoting agent for oral administration.
7 Armodafinil is the R-enantiomer of modafinil which is a mixture of the R- and S-
8 enantiomers. The chemical name for armodafinil is 2-[(R)-
9 (diphenylmethyl)sulfinyl]acetamide. The molecular formula is C₁₅H₁₅NO₂S and the
10 molecular weight is 273.35.

11
12 The chemical structure is:



13
14
15 Armodafinil is a white to off-white, crystalline powder that is very slightly soluble in
16 water, sparingly soluble in acetone and soluble in methanol. NUVIGIL tablets contain
17 50, 150 or 250 mg of armodafinil and the following inactive ingredients: croscarmellose
18 sodium, lactose, magnesium stearate, microcrystalline cellulose, povidone, and
19 pregelatinized starch.

20
21 **CLINICAL PHARMACOLOGY**

22 **Mechanism of Action and Pharmacology**

23 The precise mechanism(s) through which armodafinil (R-enantiomer) or modafinil
24 (mixture of R- and S-enantiomers) promote wakefulness is unknown. Both armodafinil
25 and modafinil have shown similar pharmacological properties in nonclinical animal and
26 in vitro studies, to the extent tested.

27

28 At pharmacologically relevant concentrations, armodafinil does not bind to or inhibit
29 several receptors and enzymes potentially relevant for sleep/wake regulation, including
30 those for serotonin, dopamine, adenosine, galanin, melatonin, melanocortin, orexin-1,
31 orphanin, PACAP or benzodiazepines, or transporters for GABA, serotonin,
32 norepinephrine, and choline or phosphodiesterase VI, COMT, GABA transaminase, and
33 tyrosine hydroxylase. Modafinil does not inhibit the activity of MAO-B or
34 phosphodiesterases II-IV.

35

36 Modafinil-induced wakefulness can be attenuated by the $\alpha 1$ -adrenergic receptor
37 antagonist, prazosin; however, modafinil is inactive in other in vitro assay systems known
38 to be responsive to α -adrenergic agonists such as the rat vas deferens preparation.

39

40 Armodafinil is not a direct- or indirect-acting dopamine receptor agonist. However, in
41 vitro, both armodafinil and modafinil bind to the dopamine transporter and inhibit
42 dopamine reuptake. For modafinil, this activity has been associated in vivo with
43 increased extracellular dopamine levels in some brain regions of animals. In genetically
44 engineered mice lacking the dopamine transporter (DAT), modafinil lacked wake-
45 promoting activity, suggesting that this activity was DAT-dependent. However, the
46 wake-promoting effects of modafinil, unlike those of amphetamine, were not antagonized
47 by the dopamine receptor antagonist haloperidol in rats. In addition, alpha-methyl-p-
48 tyrosine, a dopamine synthesis inhibitor, blocks the action of amphetamine, but does not
49 block locomotor activity induced by modafinil.

50

51 Armodafinil and modafinil have wake-promoting actions similar to sympathomimetic
52 agents including amphetamine and methylphenidate, although their pharmacologic
53 profile is not identical to that of the sympathomimetic amines. In addition to its wake-
54 promoting effects and ability to increase locomotor activity in animals, modafinil
55 produces psychoactive and euphoric effects, alterations in mood, perception, thinking,
56 and feelings typical of other CNS stimulants in humans. Modafinil has reinforcing

57 properties, as evidenced by its self-administration in monkeys previously trained to self-
58 administer cocaine; modafinil was also partially discriminated as stimulant-like.

59

60 Based on nonclinical studies, two major metabolites, acid and sulfone, of modafinil or
61 armodafinil, do not appear to contribute to the CNS-activating properties of the parent
62 compounds.

63

64 **Pharmacokinetics**

65 The active component of NUVIGIL is armodafinil, which is the longer-lived enantiomer
66 of modafinil. NUVIGIL exhibits linear time-independent kinetics following single and
67 multiple oral dose administration. Increase in systemic exposure is proportional over the
68 dose range of 50 to 400 mg. No time-dependent change in kinetics was observed through
69 12 weeks of dosing. Apparent steady state for NUVIGIL was reached within 7 days of
70 dosing. At steady state, the systemic exposure for NUVIGIL is 1.8 times the exposure
71 observed after a single dose. The concentration-time profiles of the pure R-enantiomer
72 following administration of 50 mg NUVIGIL or 100 mg PROVIGIL® (modafinil) are
73 nearly superimposable.

74

75 *Absorption*

76 NUVIGIL is readily absorbed after oral administration. The absolute oral bioavailability
77 was not determined due to the aqueous insolubility of armodafinil, which precluded
78 intravenous administration. Peak plasma concentrations are attained at approximately 2
79 hours in the fasted state. Food effect on the overall bioavailability of NUVIGIL is
80 considered minimal; however, time to reach peak concentration (t_{max}) may be delayed by
81 approximately 2-4 hours in the fed state. Since the delay in t_{max} is also associated with
82 elevated plasma levels later in time, food can potentially affect the onset and time course
83 of pharmacologic action for NUVIGIL.

84

85 *Distribution*

86 NUVIGIL has an apparent volume of distribution of approximately 42 L. Data specific
87 to armodafinil protein binding are not available. However, modafinil is moderately
88 bound to plasma protein (approximately 60%), mainly to albumin. The potential for
89 interactions of NUVIGIL with highly protein-bound drugs is considered to be minimal.

90

91 *Metabolism*

92 In vitro and in vivo data show that armodafinil undergoes hydrolytic deamidation, S-
93 oxidation, and aromatic ring hydroxylation, with subsequent glucuronide conjugation of
94 the hydroxylated products. Amide hydrolysis is the single most prominent metabolic
95 pathway, with sulfone formation by cytochrome P450 (CYP) 3A4/5 being next in
96 importance. The other oxidative products are formed too slowly in vitro to enable
97 identification of the enzyme(s) responsible. Only two metabolites reach appreciable
98 concentrations in plasma (i.e., R-modafinil acid and modafinil sulfone).

99

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

104

105 *Elimination*

106 After oral administration of NUVIGIL, armodafinil exhibits an apparent
107 monoexponential decline from the peak plasma concentration. The apparent terminal $t_{1/2}$
108 is approximately 15 hours. The oral clearance of NUVIGIL is approximately 33 mL/min.

109

110 *Drug-Drug Interactions*

111 The existence of multiple pathways for armodafinil metabolism, as well as the fact that a
112 non-CYP-related pathway is the most rapid in metabolizing armodafinil, suggest that
113 there is a low probability of substantive effects on the overall pharmacokinetic profile of
114 NUVIGIL due to CYP inhibition by concomitant medications.

115

116 In vitro data demonstrated that armodafinil shows a weak inductive response for
117 CYP1A2 and possibly CYP3A activities in a concentration-related manner and that
118 CYP2C19 activity is reversibly inhibited by armodafinil. Other CYP activities did not
119 appear to be affected by armodafinil. An in vitro study demonstrated that armodafinil is a
120 substrate of P-glycoprotein.

121

122 Chronic administration of NUVIGIL at 250 mg reduced the systemic exposure to
123 midazolam by 32% and 17% after single oral (5 mg) and intravenous (2 mg) doses,
124 respectively, suggesting that administration of NUVIGIL moderately induces CYP3A
125 activity. Drugs that are substrates for CYP3A4/5, such as cyclosporine, may require
126 dosage adjustment. (See **PRECAUTIONS, Drug Interactions**).

127

128 Chronic administration of NUVIGIL at 250 mg did not affect the pharmacokinetics of
129 caffeine (200 mg), a probe substrate for CYP1A2 activity.

130

131 Coadministration of a single 400-mg dose of NUVIGIL with omeprazole (40 mg)
132 increased systemic exposure to omeprazole by approximately 40%, indicating that
133 armodafinil moderately inhibits CYP2C19 activity. Drugs that are substrates for
134 CYP2C19 may require dosage reduction. (See **PRECAUTIONS, Drug Interactions**).

135

136 *Gender Effect:* Population pharmacokinetic analysis suggests no gender effect on the
137 pharmacokinetics of armodafinil.

138

139 *Special Populations*

140 Data specific to armodafinil in special populations are not available.

141

142 *Age Effect:* A slight decrease (~20%) in the oral clearance (CL/F) of modafinil was
143 observed in a single dose study at 200 mg in 12 subjects with a mean age of 63 years
144 (**range 53 – 72 years**), but the change was considered not likely to be clinically

145 significant. In a multiple dose study (300 mg/day) in 12 patients with a mean age of 82
146 **years (range 67 – 87 years), the mean levels of modafinil in plasma were approximately**
147 two times those historically obtained in matched younger subjects. Due to potential
148 effects from the multiple concomitant medications with which most of the patients were
149 being treated, the apparent difference in modafinil pharmacokinetics may not be
150 attributable solely to the effects of aging. However, the results suggest that the clearance
151 of modafinil may be reduced in the elderly (See **DOSAGE AND ADMINISTRATION**).

152
153 *Race Effect:* The influence of race on the pharmacokinetics of modafinil has not been
154 studied.

155
156 *Renal Impairment:* In a single dose 200 mg modafinil study, severe chronic renal failure
157 (creatinine clearance ≤ 20 mL/min) did not significantly influence the pharmacokinetics
158 of modafinil, but exposure to modafinil acid was increased 9-fold (See
159 **PRECAUTIONS**).

160
161 *Hepatic Impairment:* The pharmacokinetics and metabolism of modafinil were examined
162 in patients with cirrhosis of the liver (6 men and 3 women). Three patients had stage B or
163 B+ cirrhosis and 6 patients had stage C or C+ cirrhosis (per the Child-Pugh score
164 criteria). Clinically 8 of 9 patients were icteric and all had ascites. In these patients, the
165 oral clearance of modafinil was decreased by about 60% and the steady state
166 concentration was doubled compared to normal patients. The dose of NUVIGIL should
167 be reduced in patients with severe hepatic impairment (See **PRECAUTIONS** and
168 **DOSAGE AND ADMINISTRATION**).

169 170 **CLINICAL TRIALS**

171 The effectiveness of NUVIGIL in improving wakefulness has been established in the
172 following sleep disorders: obstructive sleep apnea/hypopnea syndrome (OSAHS),
173 narcolepsy and shift work sleep disorder (SWSD).

174

175 For each clinical trial, a p-value of ≤ 0.05 was required for statistical significance.

176

177 *Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS)*

178 The effectiveness of NUVIGIL in improving wakefulness in patients with excessive
179 sleepiness associated with OSAHS was established in two 12-week, multi-center,
180 placebo-controlled, parallel-group, double-blind studies of outpatients who met the
181 International Classification of Sleep Disorders (ICSD) criteria for OSAHS (which are
182 also consistent with the American Psychiatric Association DSM-IV criteria). These
183 criteria include either, 1) excessive sleepiness or insomnia, plus frequent episodes of
184 impaired breathing during sleep, and associated features such as loud snoring, morning
185 headaches or dry mouth upon awakening; or 2) excessive sleepiness or insomnia; and
186 polysomnography demonstrating one of the following: more than five obstructive apneas,
187 each greater than 10 seconds in duration, per hour of sleep; and one or more of the
188 following: frequent arousals from sleep associated with the apneas, bradycardia, or
189 arterial oxygen desaturation in association with the apneas. In addition, for entry into
190 these studies, all patients were required to have excessive sleepiness as demonstrated by a
191 score ≥ 10 on the Epworth Sleepiness Scale, despite treatment with continuous positive
192 airway pressure (CPAP). Evidence that CPAP was effective in reducing episodes of
193 apnea/hypopnea was required along with documentation of CPAP use.

194

195 Patients were required to be compliant with CPAP, defined as CPAP use ≥ 4 hours/night
196 on $\geq 70\%$ of nights. CPAP use continued throughout the study. In both studies, the
197 primary measures of effectiveness were 1) sleep latency, as assessed by the Maintenance
198 of Wakefulness Test (MWT) and 2) the change **in the patient's overall disease status, as**
199 measured by the Clinical Global Impression of Change (CGI-C) at the final visit. For a
200 successful trial both measures had to show statistically significant improvement.

201

202 The MWT measures latency (in minutes) to sleep onset. An extended MWT was
203 performed with test sessions at 2 hour intervals between 9AM and 7PM. The primary
204 analysis was the average of the sleep latencies from the first four test sessions (9AM to

205 3PM). For each test session, the subject was asked to attempt to remain awake without
206 using extraordinary measures. Each test session was terminated after 30 minutes if no
207 sleep occurred or immediately after sleep onset. The CGI-C is a 7-point scale, centered
208 at *No Change*, and ranging from *Very Much Worse* to *Very Much Improved*. Evaluators
209 were not given any specific guidance about the criteria they were to apply when rating
210 patients.

211

212 In the first study, a total of 395 patients with OSAHS were randomized to receive
213 NUVIGIL 150 mg/day, NUVIGIL 250 mg/day or matching placebo. Patients treated
214 with NUVIGIL showed a statistically significant improvement in the ability to remain
215 awake compared to placebo-treated patients as measured by the MWT at final visit. A
216 statistically significant greater number of patients treated with NUVIGIL showed
217 improvement in overall clinical condition as rated by the CGI-C scale at final visit. The
218 average sleep latencies (in minutes) in the MWT at baseline for the trials are shown in
219 Table 1 below, along with the average change from baseline on the MWT at final visit.
220 The percentages of patients who showed any degree of improvement on the CGI-C in the
221 clinical trials are shown in Table 2 below. The two doses of NUVIGIL produced
222 statistically significant effects of similar magnitudes on the MWT, and also on the
223 CGI-C.

224

225 In the second study, 263 patients with OSAHS were randomized to either NUVIGIL 150
226 mg/day or placebo. Patients treated with NUVIGIL showed a statistically significant
227 improvement in the ability to remain awake compared to placebo-treated patients as
228 measured by the MWT [Table 1]. A statistically significant greater number of patients
229 treated with NUVIGIL showed improvement in overall clinical condition as rated by the
230 CGI-C scale [Table 2].

231

232 Nighttime sleep measured with polysomnography was not affected by the use of
233 NUVIGIL in either study.

234

235 *Narcolepsy*

236 The effectiveness of NUVIGIL in improving wakefulness in patients with excessive
237 sleepiness (ES) associated with narcolepsy was established in one 12-week, multi-center,
238 placebo-controlled, parallel-group, double-blind study of outpatients who met the ICSD
239 criteria for narcolepsy. A total of 196 patients were randomized to receive NUVIGIL
240 150 or 250 mg/day, or matching placebo. The ICSD criteria for narcolepsy include either
241 1) recurrent daytime naps or lapses into sleep that occur almost daily for at least three
242 months, plus sudden bilateral loss of postural muscle tone in association with intense
243 emotion (cataplexy), or 2) a complaint of excessive sleepiness or sudden muscle
244 weakness with associated features: sleep paralysis, hypnagogic hallucinations, automatic
245 behaviors, disrupted major sleep episode; and polysomnography demonstrating one of the
246 following: sleep latency less than 10 minutes or rapid eye movement (REM) sleep
247 latency less than 20 minutes and a Multiple Sleep Latency Test (MSLT) that
248 demonstrates a mean sleep latency of less than 5 minutes and two or more sleep onset
249 REM periods and no medical or mental disorder accounts for the symptoms. For entry
250 into these studies, all patients were required to have objectively documented excessive
251 daytime sleepiness, via MSLT with a sleep latency of 6 minutes or less and the absence
252 of any other clinically significant active medical or psychiatric disorder. The MSLT, an
253 objective polysomnographic assessment of the **patient's ability to fall asleep in an**
254 unstimulating environment, measured latency (in minutes) to sleep onset averaged over 4
255 test sessions at 2-hour intervals. For each test session, the subject was told to lie quietly
256 and attempt to sleep. Each test session was terminated after 20 minutes if no sleep
257 occurred or immediately after sleep onset.

258

259 The primary measures of effectiveness were: 1) sleep latency as assessed by the
260 Maintenance of Wakefulness Test (MWT) and **2) the change in the patient's overall**
261 disease status, as measured by the Clinical Global Impression of Change (CGI-C) at the
262 final visit (See **CLINICAL TRIALS**, *OSAHS* section above for a description of these
263 measures). Each MWT test session was terminated after 20 minutes if no sleep occurred
264 or immediately after sleep onset in this study.

265

266 Patients treated with NUVIGIL showed a statistically significantly enhanced ability to
267 remain awake on the MWT at each dose compared to placebo at final visit [Table 1]. A
268 statistically significant greater number of patients treated with NUVIGIL at each dose
269 showed improvement in overall clinical condition as rated by the CGI-C scale at final
270 visit [Table 2].

271

272 The two doses of NUVIGIL produced statistically significant effects of similar
273 magnitudes on the CGI-C. Although a statistically significant effect on the MWT was
274 observed for each dose, the magnitude of effect was observed to be greater for the higher
275 dose.

276

277 Nighttime sleep measured with polysomnography was not affected by the use of
278 NUVIGIL.

279

280 *Shift Work Sleep Disorder (SWSD)*

281 The effectiveness of NUVIGIL in improving wakefulness in patients with excessive
282 sleepiness associated with SWSD was demonstrated in a 12-week, multi-center, double-
283 blind, placebo-controlled, parallel group, clinical trial. A total of 254 patients with
284 chronic SWSD were randomized to receive NUVIGIL 150 mg/day or placebo. All
285 patients met the ICSD criteria for chronic SWSD [which are consistent with the
286 American Psychiatric Association DSM-IV criteria for Circadian Rhythm Sleep
287 Disorder: Shift Work Type]. These criteria include 1) either: a) a primary complaint of
288 excessive sleepiness or insomnia which is temporally associated with a work period
289 (usually night work) that occurs during the habitual sleep phase, or b) polysomnography
290 and the MSLT demonstrate loss of a normal sleep-wake pattern (i.e., disturbed
291 chronobiological rhythmicity); and 2) no other medical or mental disorder accounts for
292 the symptoms, and 3) the symptoms do not meet criteria for any other sleep disorder
293 producing insomnia or excessive sleepiness (e.g., time zone change [jet lag] syndrome).

294

295 It should be noted that not all patients with a complaint of sleepiness who are also
 296 engaged in shift work meet the criteria for the diagnosis of SWSD. In the clinical trial,
 297 only patients who were symptomatic for at least 3 months were enrolled.
 298
 299 Enrolled patients were also required to work a minimum of 5 night shifts per month, have
 300 excessive sleepiness at the time of their night shifts (MSLT score \leq 6 minutes), and have
 301 daytime insomnia documented by a daytime polysomnogram (PSG).
 302
 303 The primary measures of effectiveness were 1) sleep latency, as assessed by the Multiple
 304 Sleep Latency Test (MSLT) performed during a simulated night shift at the final visit,
 305 **and 2) the change in the patient's overall** disease status, as measured by the Clinical
 306 Global Impression of Change (CGI-C) at the final visit. (See **CLINICAL TRIALS,**
 307 *Narcolepsy* and *OSAHS* sections above for description of these measures).
 308
 309 Patients treated with NUVIGIL showed a statistically significant prolongation in the time
 310 to sleep onset compared to placebo-treated patients, as measured by the nighttime MSLT
 311 at final visit [Table 1]. A statistically significant greater number of patients treated with
 312 NUVIGIL showed improvement in overall clinical condition as rated by the CGI-C scale
 313 at final visit [Table 2].
 314
 315 Daytime sleep measured with polysomnography was not affected by the use of
 316 NUVIGIL.

317
 318 **Table 1. Average Baseline Sleep Latency and Change from Baseline at Final Visit**
 319 **(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
OSAHS I	MWT	21.5	1.7	23.3	2.2	23.2	-1.7
OSAHS II	MWT	23.7	2.3	-	-	23.3	-1.3
Narcolepsy	MWT	12.1	1.3	9.5	2.6	12.5	-1.9
SWSD	MSLT	2.3	3.1	-	-	2.4	0.4

320

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

322

323

**Table 2. Clinical Global Impression of Change (CGI-C)
(Percent of Patients Who Improved at Final Visit)**

324

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

325

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

327

328 **INDICATIONS AND USAGE**

329 NUVIGIL is indicated to improve wakefulness in patients with excessive sleepiness
330 associated with obstructive sleep apnea/hypopnea syndrome, narcolepsy and shift work
331 sleep disorder.

332

333 In OSAHS, NUVIGIL is indicated as an adjunct to standard treatment(s) for the
334 underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment
335 of choice for a patient, a maximal effort to treat with CPAP for an adequate period of
336 time should be made prior to initiating NUVIGIL. If NUVIGIL is used adjunctively with
337 CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

338

339 In all cases, careful attention to the diagnosis and treatment of the underlying sleep
340 disorder(s) is of utmost importance. Prescribers should be aware that some patients may
341 have more than one sleep disorder contributing to their excessive sleepiness.

342

343 The effectiveness of NUVIGIL in long-term use (greater than 12 weeks) has not been
344 systematically evaluated in placebo-controlled trials. The physician who elects to

345 prescribe NUVIGIL for an extended time in patients should periodically re-evaluate long-
346 term usefulness for the individual patient.

347

348 **CONTRAINDICATIONS**

349 NUVIGIL is contraindicated in patients with known hypersensitivity to modafinil and
350 armodafinil or its inactive ingredients.

351 **WARNINGS**

352 **Serious Rash, including Stevens-Johnson Syndrome**

353 **Serious rash requiring hospitalization and discontinuation of treatment has been**
354 **reported in adults and children in association with the use of modafinil, a racemic**
355 **mixture of S and R modafinil (the latter is armodafinil).**

356

357 **Armodafinil has not been studied in pediatric patients in any setting and is not**
358 **approved for use in pediatric patients for any indication.**

359

360 **In clinical trials of modafinil (the racemate), the incidence of rash resulting in**
361 **discontinuation was approximately 0.8% (13 per 1,585) in pediatric patients (age**
362 **<17 years); these rashes included 1 case of possible Stevens-Johnson Syndrome**
363 **(SJS) and 1 case of apparent multi-organ hypersensitivity reaction. Several of the**
364 **cases were associated with fever and other abnormalities (e.g., vomiting,**
365 **leukopenia). The median time to rash that resulted in discontinuation was 13 days.**
366 **No such cases were observed among 380 pediatric patients who received placebo.**
367 **No serious skin rashes have been reported in adult clinical trials (0 per 4,264) of**
368 **modafinil. Rare cases of serious or life-threatening rash, including SJS, Toxic**
369 **Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic**
370 **Symptoms (DRESS) have been reported in adults and children in worldwide post-**
371 **marketing experience. The reporting rate of TEN and SJS associated with**
372 **modafinil use, which is generally accepted to be an underestimate due to**
373 **underreporting, exceeds the background incidence rate. Estimates of the**

374 **background incidence rate for these serious skin reactions in the general population**
375 **range between 1 to 2 cases per million-person years.**

376

377 **No serious skin rashes have been reported in adult clinical trials (0 per 1,595) of**
378 **armodafinil. However, because armodafinil is the R isomer of racemic modafinil, a**
379 **similar risk of serious rash with armodafinil cannot be ruled out.**

380

381 **There are no factors that are known to predict the risk of occurrence or the severity**
382 **of rash associated with modafinil or armodafinil. Nearly all cases of serious rash**
383 **associated with modafinil occurred within 1 to 5 weeks after treatment initiation.**
384 **However, isolated cases have been reported after prolonged treatment (e.g., 3**
385 **months). Accordingly, duration of therapy cannot be relied upon as a means to**
386 **predict the potential risk heralded by the first appearance of a rash.**

387

388 **Although benign rashes also occur with armodafinil, it is not possible to reliably**
389 **predict which rashes will prove to be serious. Accordingly, armodafinil should**
390 **ordinarily be discontinued at the first sign of rash, unless the rash is clearly not**
391 **drug-related. Discontinuation of treatment may not prevent a rash from becoming**
392 **life-threatening or permanently disabling or disfiguring.**

393

394 **Angioedema and anaphylactoid reactions**

395 **One serious case of angioedema and one case of hypersensitivity (with rash, dysphagia,**
396 **and bronchospasm), were observed among 1,595 patients treated with armodafinil.**
397 **Patients should be advised to discontinue therapy and immediately report to their**
398 **physician any signs or symptoms suggesting angioedema or anaphylaxis (e.g., swelling of**
399 **face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness).**

400

401 **Multi-organ Hypersensitivity Reactions**

402 **Multi-organ hypersensitivity reactions, including at least one fatality in postmarketing**
403 **experience, have occurred in close temporal association (median time to detection 13**

404 days: range 4-33) to the initiation of modafinil. A similar risk of multi-organ
405 hypersensitivity reactions with armodafinil cannot be ruled out.

406

407 Although there have been a limited number of reports, multi-organ hypersensitivity
408 reactions may result in hospitalization or be life-threatening. There are no factors that are
409 known to predict the risk of occurrence or the severity of multi-organ hypersensitivity
410 reactions associated with modafinil. Signs and symptoms of this disorder were diverse;
411 however, patients typically, although not exclusively, presented with fever and rash
412 associated with other organ system involvement. Other associated manifestations
413 included myocarditis, hepatitis, liver function test abnormalities, hematological
414 abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritis, and asthenia.
415 Because multi-organ hypersensitivity is variable in its expression, other organ system
416 symptoms and signs, not noted here, may occur.

417

418 If a multi-organ hypersensitivity reaction is suspected, NUVIGIL should be discontinued.
419 Although there are no case reports to indicate cross-sensitivity with other drugs that
420 produce this syndrome, the experience with drugs associated with multi-organ
421 hypersensitivity would indicate this to be a possibility.

422

423 **Persistent Sleepiness**

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

431

432 **Psychiatric Symptoms**

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

437

438 Postmarketing adverse events associated with the use of modafinil have included mania,
439 delusions, hallucinations, and suicidal ideation, some resulting in hospitalization. Many,
440 but not all, patients had a prior psychiatric history. One healthy male volunteer
441 developed ideas of reference, paranoid delusions, and auditory hallucinations in
442 association with multiple daily 600 mg doses of modafinil and sleep deprivation. There
443 was no evidence of psychosis 36 hours after drug discontinuation.

444

445 In the controlled trial NUVIGIL database, anxiety, agitation, nervousness, and irritability
446 were reasons for treatment discontinuation more often in patients on NUVIGIL compared
447 to placebo (NUVIGIL 1.2% and placebo 0.3%). In the NUVIGIL controlled studies,
448 depression was also a reason for treatment discontinuation more often in patients on
449 NUVIGIL compared to placebo (NUVIGIL 0.6% and placebo 0.2%). Two cases of
450 suicide ideation were observed in clinical trials. Caution should be exercised when
451 NUVIGIL is given to patients with a history of psychosis, depression, or mania. If
452 psychiatric symptoms develop in association with NUVIGIL administration, consider
453 discontinuing NUVIGIL.

454

455 **PRECAUTIONS**

456 *Diagnosis of Sleep Disorders*

457 NUVIGIL should be used only in patients who have had a complete evaluation of their
458 excessive sleepiness, and in whom a diagnosis of either narcolepsy, OSAHS, and/or
459 SWSD has been made in accordance with ICSD or DSM diagnostic criteria (See
460 **CLINICAL TRIALS**). Such an evaluation usually consists of a complete history and
461 physical examination, and it may be supplemented with testing in a laboratory setting.

462 Some patients may have more than one sleep disorder contributing to their excessive
463 sleepiness (e.g., OSAHS and SWSD coincident in the same patient).

464

465 *CPAP Use in Patients with OSAHS*

466 In OSAHS, NUVIGIL is indicated as an adjunct to standard treatment(s) for the
467 underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment
468 of choice for a patient, a maximal effort to treat with CPAP for an adequate period of
469 time should be made prior to initiating NUVIGIL. If NUVIGIL is used adjunctively with
470 CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.
471 There was a slight trend for reduced CPAP use over time (mean reduction of 18 minutes
472 for patients treated with NUVIGIL and a 6 minute reduction for placebo-treated patients
473 from a mean baseline use of 6.9 hours per night) in NUVIGIL trials.

474

475 *General*

476 Although NUVIGIL has not been shown to produce functional impairment, any drug
477 affecting the CNS may alter judgment, thinking or motor skills. Patients should be
478 cautioned about operating an automobile or other hazardous machinery until they are
479 reasonably certain that NUVIGIL therapy will not adversely affect their ability to engage
480 in such activities.

481

482 *Cardiovascular System*

483 NUVIGIL has not been evaluated or used to any appreciable extent in patients with a
484 recent history of myocardial infarction or unstable angina, and such patients should be
485 treated with caution.

486

487 In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations,
488 dyspnea and transient ischemic T-wave changes on ECG were observed in three subjects
489 in association with mitral valve prolapse or left ventricular hypertrophy. It is
490 recommended that NUVIGIL tablets not be used in patients with a history of left
491 ventricular hypertrophy or in patients with mitral valve prolapse who have experienced

492 the mitral valve prolapse syndrome when previously receiving CNS stimulants. Signs of
493 mitral valve prolapse syndrome include but are not limited to ischemic ECG changes,
494 chest pain, or arrhythmia. If new onset of any of these symptoms occurs, consider
495 cardiac evaluation.

496

497 Blood pressure monitoring in short-term (≤ 3 months) controlled trials showed only small
498 average increases in mean systolic and diastolic blood pressure in patients receiving
499 NUVIGIL as compared to placebo (1.2 to 4.3 mmHg in the various experimental groups).
500 There was also a slightly greater proportion of patients on NUVIGIL requiring new or
501 increased use of antihypertensive medications (2.9%) compared to patients on placebo
502 (1.8%). Increased monitoring of blood pressure may be appropriate in patients on
503 NUVIGIL.

504

505 *Patients Using Steroidal Contraceptives*

506 The effectiveness of steroidal contraceptives may be reduced when used with NUVIGIL
507 and for one month after discontinuation of therapy (See **PRECAUTIONS, Drug**
508 **Interactions**). Alternative or concomitant methods of contraception are recommended
509 for patients treated with NUVIGIL and for one month after discontinuation of NUVIGIL
510 treatment.

511

512 *Patients Using Cyclosporine*

513 The blood levels of cyclosporine may be reduced when used with NUVIGIL (See
514 **PRECAUTIONS, Drug Interactions**). Monitoring of circulating cyclosporine
515 concentrations and appropriate dosage adjustment for cyclosporine should be considered
516 when these drugs are used concomitantly.

517

518 *Patients with Severe Hepatic Impairment*

519 In patients with severe hepatic impairment, with or without cirrhosis (See **CLINICAL**
520 **PHARMACOLOGY**), NUVIGIL should be administered at a reduced dose (See
521 **DOSAGE AND ADMINISTRATION**).

522

523 *Patients with Severe Renal Impairment*

524 There is inadequate information to determine safety and efficacy of dosing in patients
525 with severe renal impairment (For pharmacokinetics in renal impairment, see **CLINICAL**
526 **PHARMACOLOGY**).

527

528 *Elderly Patients*

529 In elderly patients, elimination of armodafinil and its metabolites may be reduced as a
530 consequence of aging. Therefore, consideration should be given to the use of lower doses
531 in this population (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND**
532 **ADMINISTRATION**).

533

534 *Information for Patients*

535 Physicians are advised to discuss the following issues with patients for whom they
536 prescribe NUVIGIL.

537

538 NUVIGIL is indicated for patients who have abnormal levels of sleepiness. NUVIGIL
539 has been shown to improve, but not eliminate, this abnormal tendency to fall asleep.
540 Therefore, patients should not alter their previous behavior with regard to potentially
541 dangerous activities (e.g., driving, operating machinery) or other activities requiring
542 appropriate levels of wakefulness, until and unless treatment with NUVIGIL has been
543 shown to produce levels of wakefulness that permit such activities. Patients should be
544 advised that NUVIGIL is not a replacement for sleep.

545

546 Patients should be informed that it may be critical that they continue to take their
547 previously prescribed treatments (e.g., patients with OSAHS receiving CPAP should
548 continue to do so).

549

550 Patients should be informed of the availability of a patient information leaflet, and they
551 should be instructed to read the leaflet prior to taking NUVIGIL. See Patient Information
552 at the end of this labeling for the text of the leaflet provided for patients.

553

554 Patients should be advised to contact their physician if they experience rash, depression,
555 anxiety, or signs of psychosis or mania.

556

557 *Pregnancy*

558 Patients should be advised to notify their physician if they become pregnant or intend to
559 become pregnant during therapy. Patients should be cautioned regarding the potential
560 increased risk of pregnancy when using steroidal contraceptives (including depot or
561 implantable contraceptives) with NUVIGIL and for one month after discontinuation of
562 therapy (See *Carcinogenesis, Mutagenesis, Impairment of Fertility* and **Pregnancy**).

563

564 *Nursing*

565 Patients should be advised to notify their physician if they are breastfeeding an infant.

566

567 *Concomitant Medication*

568 Patients should be advised to inform their physician if they are taking, or plan to take, any
569 prescription or over-the-counter drugs, because of the potential for interactions between
570 NUVIGIL and other drugs.

571

572 *Alcohol*

573 Patients should be advised that the use of NUVIGIL in combination with alcohol has not
574 been studied. Patients should be advised that it is prudent to avoid alcohol while taking
575 NUVIGIL.

576

577 *Allergic Reactions*

578 Patients should be advised to stop taking NUVIGIL and to notify their physician if they
579 develop a rash, hives, mouth sores, blisters, peeling skin, trouble swallowing or breathing
580 or a related allergic phenomenon.

581

582 **Drug Interactions**

583

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

586

587 Due to the partial involvement of CYP3A enzymes in the metabolic elimination of
588 armodafinil, coadministration of potent inducers of CYP3A4/5 (e.g., carbamazepine,
589 phenobarbital, rifampin) or inhibitors of CYP3A4/5 (e.g. ketoconazole, erythromycin)
590 could alter the plasma levels of armodafinil.

591

592 *The Potential of NUVIGIL to Alter the Metabolism of Other Drugs by Enzyme Induction*
593 *or Inhibition*

594

595 *Drugs Metabolized by CYP1A2*

596 In vitro data demonstrated that armodafinil shows a weak inductive response for
597 CYP1A2 and possibly CYP3A activities in a concentration related manner and
598 demonstrated that CYP2C19 activity is reversibly inhibited by armodafinil. However, the
599 effect on CYP1A2 activity was not observed clinically in an interaction study performed
600 with caffeine (See **Pharmacokinetics, Drug-Drug Interactions**).

601

602 *Drugs Metabolized by CYP3A4/5 (e.g., cyclosporine, ethinyl estradiol, midazolam and*
603 *triazolam)*

604 Chronic administration of NUVIGIL resulted in moderate induction of CYP3A activity.
605 Hence, the effectiveness of drugs that are substrates for CYP3A enzymes (e.g.,
606 cyclosporine, ethinyl estradiol, midazolam and triazolam) may be reduced after
607 initiation of concurrent treatment with NUVIGIL. A 32% reduction in systemic exposure
608 of oral midazolam was seen upon concomitant administration of armodafinil with
609 midazolam. Dose adjustment may be required (See **Pharmacokinetics, Drug-Drug**
610 **Interactions**). Such effects (reduced concentrations) were also seen upon concomitant
611 administration of modafinil with cyclosporine, ethinyl estradiol, and triazolam.

612

613 *Drugs Metabolized by CYP2C19 (e.g., omeprazole, diazepam, phenytoin, and*
614 *propranolol)*

615 Administration of NUVIGIL resulted in moderate inhibition of CYP2C19 activity.
616 Hence, dosage reduction may be required for some drugs that are substrates for
617 CYP2C19 (e.g. phenytoin, diazepam, and propranolol, omeprazole and clomipramine)
618 when used concurrently with NUVIGIL. A 40% increase in exposure was seen upon
619 concomitant administration of armodafinil with omeprazole. (See **Pharmacokinetics,**
620 *Drug-Drug Interactions*).

621

622 *Interactions with CNS Active Drugs*

623 Data specific to armodafinil drug-drug interaction potential with CNS active drugs are
624 not available. However, the following available drug-drug interaction information on
625 modafinil should be applicable to armodafinil (See **DESCRIPTION** and **CLINICAL**
626 **PHARMACOLOGY**).

627

628 Concomitant administration of modafinil with methylphenidate, or dextroamphetamine
629 produced no significant alterations on the pharmacokinetic profile of modafinil or either
630 stimulant, even though the absorption of modafinil was delayed for approximately one
631 hour.

632

633 Concomitant modafinil or clomipramine did not alter the PK profile of either drug;
634 however, one incident of increased levels of clomipramine and its active metabolite
635 desmethylclomipramine was reported in a patient with narcolepsy during treatment with
636 modafinil.

637

638 *Data specific to armodafinil or modafinil drug-drug interaction potential with*
639 *Monoamine Oxidase (MAO) inhibitors are not available. Therefore, caution should be*
640 *used when concomitantly administering MAO inhibitors and NUVIGIL.*

641

642 Interactions with Other Drugs

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

646

647 Warfarin - Concomitant administration of modafinil with warfarin did not produce
648 significant changes in the pharmacokinetic profiles of R- and S-warfarin. However, since
649 only a single dose of warfarin was tested in this study, a pharmacodynamic interaction
650 cannot be ruled out. Therefore, more frequent monitoring of prothrombin times/INR
651 should be considered whenever NUVIGIL is coadministered with warfarin.

652

653 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

654 *Carcinogenesis*

655 Carcinogenicity studies have not been conducted with armodafinil alone.
656 Carcinogenicity studies were conducted in which modafinil was administered in the diet
657 to mice for 78 weeks and to rats for 104 weeks at doses of 6, 30, and 60 mg/kg/day. The
658 highest dose studied represents 1.5 (mouse) or 3 (rat) times greater than the
659 recommended adult human daily dose of modafinil (200 mg) on a mg/m² basis. There
660 was no evidence of tumorigenesis associated with modafinil administration in these
661 studies. However, since the mouse study used an inadequate high dose that was not
662 representative of a maximum tolerated dose, a subsequent carcinogenicity study was
663 conducted in the Tg.AC transgenic mouse. Doses evaluated in the Tg.AC assay were 125,
664 250, and 500 mg/kg/day, administered dermally. There was no evidence of
665 tumorigenicity associated with modafinil administration; however, this dermal model
666 may not adequately assess the carcinogenic potential of an orally administered drug.

667

668 *Mutagenesis*

669 Armodafinil was evaluated in an in vitro bacterial reverse mutation assay and in an in
670 vitro mammalian chromosomal aberration assay in human lymphocytes. Armodafinil
671 was negative in these assays, both in the absence and presence of metabolic activation.

672

673 Modafinil demonstrated no evidence of mutagenic or clastogenic potential in a series of
674 in vitro (i.e., bacterial reverse mutation assay, mouse lymphoma tk assay, chromosomal
675 aberration assay in human lymphocytes, cell transformation assay in BALB/3T3 mouse
676 embryo cells) assays in the absence or presence of metabolic activation, or in vivo
677 (mouse bone marrow micronucleus) assays. Modafinil was also negative in the
678 unscheduled DNA synthesis assay in rat hepatocytes.

679

680 *Impairment of Fertility*

681 A fertility and early embryonic development (to implantation) study was not conducted
682 with armodafinil alone.

683

684 Oral administration of modafinil (doses of up to 480 mg/kg/day) to male and female rats
685 prior to and throughout mating, and continuing in females through day 7 of gestation
686 produced an increase in the time to mate at the highest dose; no effects were observed on
687 other fertility or reproductive parameters. The no-effect dose of 240 mg/kg/day was
688 associated with a plasma modafinil exposure (AUC) approximately equal to that in
689 humans at the recommended dose of 200 mg.

690

691 **Pregnancy**

692 Pregnancy Category C.

693 In studies conducted in rats (armodafinil, modafinil) and rabbits (modafinil),
694 developmental toxicity was observed at clinically relevant exposures.

695

696 Oral administration of armodafinil (60, 200, or 600 mg/kg/day) to pregnant rats
697 throughout the period of organogenesis resulted in increased incidences of fetal visceral
698 and skeletal variations at the intermediate dose or greater and decreased fetal body
699 weights at the highest dose. The no-effect dose for rat embryofetal developmental
700 toxicity was associated with a plasma armodafinil exposure (AUC) approximately 0.03
701 times the AUC in humans at the maximum recommended daily dose of 250 mg.

702

703 Modafinil (50, 100, or 200 mg/kg/day) administered orally to pregnant rats throughout
704 the period of organogenesis caused, in the absence of maternal toxicity, an increase in
705 resorptions and an increased incidence of visceral and skeletal variations in the offspring
706 at the highest dose. The higher no-effect dose for rat embryofetal developmental toxicity
707 was associated with a plasma modafinil exposure approximately 0.5 times the AUC in
708 humans at the recommended daily dose (RHD) of 200 mg. However, in a subsequent
709 study of up to 480 mg/kg/day (plasma modafinil exposure approximately 2 times the
710 AUC in humans at the RHD) no adverse effects on embryofetal development were
711 observed.

712

713 Modafinil administered orally to pregnant rabbits throughout the period of organogenesis
714 at doses of up to 100 mg/kg/day (plasma modafinil AUC approximately equal to the
715 AUC in humans at the RHD) had no effect on embryofetal development; however, the
716 doses used were too low to adequately assess the effects on modafinil on embryofetal
717 development. In a subsequent developmental toxicity study evaluating doses of 45, 90,
718 and 180 mg/kg/day in pregnant rabbits, the incidences of fetal structural alterations and
719 embryofetal death were increased at the highest dose. The highest no-effect dose for
720 developmental toxicity was associated with a plasma modafinil AUC approximately
721 equal to the AUC in humans at the RHD.

722

723 Modafinil administration to rats throughout gestation and lactation at oral doses of up to
724 200 mg/kg/day resulted in decreased viability in the offspring at doses greater than 20
725 mg/kg/day (plasma modafinil AUC approximately 0.1 times the AUC in humans at the
726 RHD). No effects on postnatal developmental and neurobehavioral parameters were
727 observed in surviving offspring.

728

729 There are no adequate and well-controlled studies of either armodafinil or modafinil in
730 pregnant women. Two cases of intrauterine growth retardation and one case of
731 spontaneous abortion have been reported in association with armodafinil and modafinil.
732 Although the pharmacology of armodafinil is not identical to that of the
733 sympathomimetic amines, it does share some pharmacologic properties with this class.

734 Certain of these drugs have been associated with intrauterine growth retardation and
735 spontaneous abortions. Whether the cases reported with armodafinil are drug-related is
736 unknown.

737

738 Armodafinil or modafinil should be used during pregnancy only if the potential benefit
739 justifies the potential risk to the fetus.

740

741 **Labor and Delivery**

742 The effect of armodafinil on labor and delivery in humans has not been systematically
743 investigated.

744

745 **Nursing Mothers**

746 It is not known whether armodafinil or its metabolites are excreted in human milk.

747 Because many drugs are excreted in human milk, caution should be exercised when

748 NUVIGIL tablets are administered to a nursing woman.

749

750 **PEDIATRIC USE**

751 Safety and effectiveness of armodafinil use in individuals below 17 years of age have not

752 been established. Serious rash has been seen in pediatric patients receiving modafinil

753 (See **WARNINGS, Serious Rash, including Stevens-Johnson Syndrome**).

754

755 **GERIATRIC USE**

756 Safety and effectiveness in individuals above 65 years of age have not been established.

757

758 **ADVERSE REACTIONS**

759 Armodafinil has been evaluated for safety in over 1100 patients with excessive sleepiness

760 associated with primary disorders of sleep and wakefulness. In clinical trials, NUVIGIL

761 has been found to be generally well tolerated and most adverse experiences were mild to

762 moderate.

763

764 In the placebo-controlled clinical studies, the most commonly observed adverse events

765 (≥ 5%) associated with the use of NUVIGIL occurring more frequently than in the
 766 placebo-treated patients were headache, nausea, dizziness, and insomnia. The adverse
 767 event profile was similar across the studies.

768

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

773

774 *Incidence in Controlled Trials*

775 The following table (Table 4) presents the adverse experiences that occurred at a rate of
 776 1% or more and were more frequent in patients treated with NUVIGIL than in placebo
 777 group patients in the placebo-controlled clinical trials.

778

779 The prescriber should be aware that the figures provided below cannot be used to predict
 780 the frequency of adverse experiences in the course of usual medical practice, where
 781 patient characteristics and other factors may differ from those occurring during clinical
 782 studies. Similarly, the cited frequencies cannot be directly compared with figures
 783 obtained from other clinical investigations involving different treatments, uses, or
 784 investigators. Review of these frequencies, however, provides prescribers with a basis to
 785 estimate the relative contribution of drug and non-drug factors to the incidence of adverse
 786 events in the population studied.

787

788 **Table 3. Incidence > 1% (In Percent) Of Treatment-Emergent Adverse**
 789 **Experiences In Parallel-Group, Placebo-Controlled Clinical Trials^a In OSAHS,**
 790 **Narcolepsy and SWSD With NUVIGIL (150 mg and 250 mg)**

System Organ Class MedDRA preferred term	NUVIGIL (Percent, N=645)	Placebo (Percent, N=445)
Cardiac Disorders		
Palpitations	2	1
Gastrointestinal Disorders		
Nausea	7	3
Diarrhea	4	2

FDA Approved Labeling Text for NDA 21-875/NUVIGIL™ (armodafinil) Tablets
 Approved Labeling dated June 15, 2007

System Organ Class MedDRA preferred term	NUVIGIL (Percent, N=645)	Placebo (Percent, N=445)
Dry Mouth	4	1
Dyspepsia	2	0
Abdominal Pain Upper	2	1
Constipation	1	0
Vomiting	1	0
Loose Stools	1	0
General Disorders And Administration Site Conditions		
Fatigue	2	1
Thirst	1	0
Influenza-Like Illness	1	0
Pain	1	0
Pyrexia	1	0
Immune System Disorders		
Seasonal Allergy	1	0
Investigations		
Gamma-Glutamyltransferase Increased	1	0
Heart Rate Increased	1	0
Metabolism And Nutrition Disorders		
Anorexia	1	0
Decreased Appetite	1	0
Nervous System Disorders		
Headache	17	9
Dizziness	5	2
Disturbance In Attention	1	0
Tremor	1	0
Migraine	1	0
Paraesthesia	1	0

System Organ Class MedDRA preferred term	NUVIGIL (Percent, N=645)	Placebo (Percent, N=445)
Psychiatric Disorders		
Insomnia	5	1
Anxiety	4	1
Depression	2	0
Agitation	1	0
Nervousness	1	0
Depressed Mood	1	0
Renal And Urinary Disorders		
Polyuria	1	0
Respiratory, Thoracic And Mediastinal Disorders		
Dyspnea	1	0
Skin And Subcutaneous Tissue Disorders		
Rash	2	0
Contact Dermatitis	1	0
Hyperhidrosis	1	0

791

792 * Four double-blind, placebo-controlled clinical studies in SWSD, OSAHS, and narcolepsy; incidence is
 793 rounded to the nearest whole percent. Included are only those events for which NUVIGIL incidence is
 794 greater than that of placebo.

795

796 *Dose Dependency of Adverse Events*

797 In the placebo-controlled clinical trials which compared doses of 150 mg/day and 250
 798 mg/day of NUVIGIL and placebo, the only adverse events that appeared to be dose-
 799 related were headache, rash, depression, dry mouth, insomnia, and nausea.

800

801 **Table 4. Incidence (In Percent) Of Dose-Dependent, Treatment-Emergent Adverse**
 802 **Experiences By Dose and By Treatment In Parallel-Group, Placebo-Controlled**
 803 **Clinical Trials^a In OSAHS, Narcolepsy and SWSD With**
 804 **NUVIGIL (150 mg and 250 mg)**

System Organ Class MedDRA preferred term,	NUVIGIL 250 mg (Percent, N=198)	NUVIGIL 150 mg (Percent, N=447)	NUVIGIL Combined (Percent, N=645)	Placebo (Percent, N=445)
Gastrointestinal Disorders				
Nausea	9	6	7	3

Dry Mouth	7	2	4	<1
Nervous System Disorders				
Headache	23	14	17	9
Psychiatric Disorders				
Insomnia	6	4	5	1
Depression	3	1	2	<1
Skin And Subcutaneous Tissue Disorders				
Rash	4	1	2	<1

805

806 Four double-blind, placebo-controlled clinical studies in SWSD, OSAHS, and narcolepsy.

807

808 *Vital Sign Changes*

809 There were small, but consistent, increases in average values for mean systolic and
 810 diastolic blood pressure in controlled trials (See **PRECAUTIONS**). There was a small,
 811 but consistent, average increase in pulse rate over placebo in controlled trials. This
 812 increase varied from 0.9 to 3.5 BPM.

813

814 *Laboratory Changes*

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

825

826 *ECG Changes*

827 No pattern of ECG abnormalities could be attributed to NUVIGIL administration in
 828 placebo-controlled clinical trials.

829

830 **DRUG ABUSE AND DEPENDENCE**

831 **Controlled Substance Class**

832 Armodafinil (NUVIGIL) is a Schedule IV controlled substance.

833

834 **Abuse Potential and Dependence**

835 Although the abuse potential of armodafinil has not been specifically studied, its abuse
836 potential is likely to be similar to that of modafinil (PROVIGIL). In humans, modafinil
837 produces psychoactive and euphoric effects, alterations in mood, perception, thinking and
838 feelings typical of other CNS stimulants. In in vitro binding studies, modafinil binds to
839 the dopamine reuptake site and causes an increase in extracellular dopamine, but no
840 increase in dopamine release. Modafinil is reinforcing, as evidenced by its self-
841 administration in monkeys previously trained to self-administer cocaine. In some studies,
842 modafinil was also partially discriminated as stimulant-like. Physicians should follow
843 patients closely, especially those with a history of drug and/or stimulant (e.g.,
844 methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs
845 of misuse or abuse (e.g., incrementation of doses or drug-seeking behavior).

846

847 The abuse potential of modafinil (200, 400, and 800 mg) was assessed relative to
848 methylphenidate (45 and 90 mg) in an inpatient study in individuals experienced with
849 drugs of abuse. Results from this clinical study demonstrated that modafinil produced
850 psychoactive and euphoric effects and feelings consistent with other scheduled CNS
851 stimulants (methylphenidate).

852

853 **OVERDOSAGE**

854 **Human Experience**

855 There were no overdoses reported in the NUVIGIL clinical studies.

856 Symptoms of NUVIGIL overdose are likely to be similar to those of modafinil.

857 Overdose in modafinil clinical trials included excitation or agitation, insomnia, and slight
858 or moderate elevations in hemodynamic parameters. From post-marketing experience
859 with modafinil, there have been no reports of fatal overdoses involving modafinil alone

860 (doses up to 12 grams). Overdoses involving multiple drugs, including modafinil, have
861 resulted in fatal outcomes. Symptoms most often accompanying modafinil overdose,
862 alone or in combination with other drugs have included; insomnia; central nervous
863 system symptoms such as restlessness, disorientation, confusion, excitation and
864 hallucination; digestive changes such as nausea and diarrhea; and cardiovascular changes
865 such as tachycardia, bradycardia, hypertension and chest pain.

866

867 **Overdose Management**

868 No specific antidote exists for the toxic effects of a NUVIGIL overdose. Such overdoses
869 should be managed with primarily supportive care, including cardiovascular monitoring.
870 If there are no contraindications, induced emesis or gastric lavage should be considered.
871 There are no data to suggest the utility of dialysis or urinary acidification or alkalinization
872 in enhancing drug elimination. The physician should consider contacting a
873 poison-control center for advice in the treatment of any overdose.

874

875 **DOSAGE AND ADMINISTRATION**

876 **Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS) and Narcolepsy**

877 The recommended dose of NUVIGIL for patients with OSAHS or narcolepsy is 150 mg
878 or 250 mg given as a single dose in the morning. In patients with OSAHS, doses up to
879 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent
880 evidence that this dose confers additional benefit beyond that of the 150 mg/day dose
881 (See **CLINICAL PHARMACOLOGY** and **CLINICAL TRIALS**).

882

883 **Shift Work Sleep Disorder (SWSD)**

884 The recommended dose of NUVIGIL for patients with SWSD is 150 mg given daily
885 approximately 1 hour prior to the start of their work shift.

886

887 Dosage adjustment should be considered for concomitant medications that are substrates
888 for CYP3A4/5, such as steroidal contraceptives, triazolam, and cyclosporine (See
889 **PRECAUTIONS, Drug Interactions**).

890

891 Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam,
892 propranolol, and phenytoin may have prolonged elimination upon coadministration with
893 NUVIGIL and may require dosage reduction and monitoring for toxicity (See
894 **PRECAUTIONS, Drug Interactions**).

895

896 In patients with severe hepatic impairment, NUVIGIL should be administered at a
897 reduced dose (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

898

899 There is inadequate information to determine safety and efficacy of dosing in patients
900 with severe renal impairment (See **CLINICAL PHARMACOLOGY** and
901 **PRECAUTIONS**).

902

903 In elderly patients, elimination of armodafinil and its metabolites may be reduced as a
904 consequence of aging. Therefore, consideration should be given to the use of lower doses
905 in this population (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

906

907 **HOW SUPPLIED:**

908

909 **NUVIGIL™ (armodafinil) Tablets [C-IV]**

910 **50 mg:** Each round, white, uncoated tablet is debossed with "C" on one side and "205"
911 on the other.

912 NDC 63459-205-60 - Bottles of 60

913 **150 mg:** Each oval, white, uncoated tablet is debossed with "C" on one side and "215"
914 on the other.

915 NDC 63459-215-60 - Bottles of 60

916 **250 mg:** Each oval, white, uncoated tablet is debossed with "C" on one side and "225" on
917 the other.

918 NDC 63459-225-60 - Bottles of 60

919

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

921

922 Manufactured for:
923 **Cephalon, Inc.**
924 Frazer, PA 19355
925 U.S. Patent Nos. RE37,516; 4,927,855
926
927 © Cephalon, Inc., 2007 All rights reserved
928
929 June 2007
930 Proposed NUV-001

Appears This Way
On Original

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PATIENT INFORMATION
NUVIGIL™ (nu-vij-el) Tablets [C-IV]

Generic name: armodafinil

Read the Patient Information that comes with NUVIGIL before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

What is the most important information I should know about NUVIGIL?

1. NUVIGIL may cause you to have a serious rash or a serious allergic reaction. Stop NUVIGIL and call your doctor right away or get emergency treatment if you have any of the following:

- skin rash, hives, sores in your mouth, or your skin blisters and peels
- swelling of your face, eyes, lips, tongue, or throat
- trouble swallowing or breathing
- hoarse voice

2. NUVIGIL has not been studied in children under the age of 17. NUVIGIL is not approved for children for any condition.

What is NUVIGIL?

NUVIGIL is a prescription medicine used to improve awakesness in adults who are very sleepy due to one of the following diagnosed sleep problems:

- shift work sleep disorder (SWSD)
- obstructive sleep apnea/hypopnea syndrome (OSAHS). NUVIGIL is used along with other medical treatments for this sleep problem. NUVIGIL is not a replacement for your CPAP machine. It is important that you continue to use your CPAP machine while sleeping.
- narcolepsy

962 You should be diagnosed with one of these sleep disorders before taking NUVIGIL.

963 Sleepiness can be a symptom of other medical conditions that need to be treated.

964

965 • NUVIGIL will not cure the above sleep disorders. NUVIGIL may help the sleepiness
966 caused by these conditions, but it may not stop all your sleepiness.

967 • NUVIGIL does not take the place of getting enough sleep.

968 • Follow your doctor's advice about good sleep habits and using other treatments.

969

970 NUVIGIL is a federally controlled substance (C-IV) because it can be abused or
971 lead to dependence. Keep NUVIGIL in a safe place to prevent misuse and abuse.
972 Selling or giving away NUVIGIL may harm others, and is against the law. Tell your
973 doctor if you have ever abused or been dependent on alcohol, prescription medicines
974 or street drugs.

974 **Who should not take NUVIGIL?**

975 Do not take NUVIGIL if you:

976 • are allergic to any of its ingredients. The active ingredient is armodafinil. See the
977 end of this leaflet for a complete list of ingredients.

978 • have had a rash or allergic reaction to modafinil, the active ingredient in PROVIGIL,
979 because these medicines are very similar.

980

981 It is not known if NUVIGIL works in or is safe for use in children under 17 years old.

982

983 **What should I tell my doctor before starting NUVIGIL?**

984 **Tell your doctor about all of your health conditions including, if you:**

985 • have a history of mental health problems

986 • have heart problems or had a heart attack

987 • have high blood pressure

988 • have liver or kidney problems

989 • have a history of drug or alcohol abuse or addiction

990 • have ever had a mental problem called psychosis.

991 • are pregnant or planning to become pregnant. It is not known if NUVIGIL may harm

992 your unborn baby.

993 • are breastfeeding. It is not known if NUVIGIL passes into your milk or if it can harm
994 your baby.

995

996 Tell your doctor about all the medicines you take, including prescription and non-
997 prescription medicines, vitamins, and herbal supplements. NUVIGIL and many other
998 medicines can interact with each other, sometimes causing side effects. NUVIGIL may
999 affect the way other medicines work, and other medicines may affect how NUVIGIL
1000 works. Especially, tell your doctor if you use a hormonal birth control method.

1001 NUVIGIL can affect hormonal birth control methods. Hormonal birth control methods
1002 include pills, shots, implants, patches, vaginal rings, and intrauterine devices (IUDs).

1003 Women who use hormonal birth control with NUVIGIL may have a higher chance for
1004 getting pregnant while taking NUVIGIL, and for one month after stopping NUVIGIL.

1005 Talk to your doctor about birth control methods that are right for you while using
1006 NUVIGIL.

1007

1008 Keep a list of all the medicines you take. Your doctor or pharmacist will tell you if it is
1009 safe to take NUVIGIL and other medicines together. Do not take other medicines with
1010 NUVIGIL unless your doctor has told you it is okay.

1011

1012 **How should I take NUVIGIL?**

1013 • Take NUVIGIL exactly as prescribed by your doctor. Your doctor will prescribe the
1014 dose of NUVIGIL that is right for you. Do not change your dose of NUVIGIL
1015 without talking to your doctor. Do not take more NUVIGIL than prescribed.

1016 • Your doctor will tell you the right time of day to take NUVIGIL.

1017 ○ Patients with narcolepsy or OSAHS usually take one dose of NUVIGIL every day
1018 in the morning.

1019 ○ Patients with SWSD usually take NUVIGIL about 1 hour before their work shift.

1020 Do not change the time of day you take NUVIGIL unless you have talked to your
1021 doctor. If you take NUVIGIL too close to your bedtime, you may find it harder to
1022 go to sleep.

- 1023 • If you take more than your prescribed dose or overdose, call your doctor or poison
1024 control center right away.

1025

1026 **What should I avoid while taking NUVIGIL?**

- 1027 • Do not drive a car or do other dangerous activities until you know how NUVIGIL
1028 affects you. People with sleep disorders should always be careful about doing things
1029 that could be dangerous. Do not change your daily habits until your doctor tells you
1030 it is okay.

- 1031 • Avoid drinking alcohol.

1032

1033 **What are the possible side effects of NUVIGIL?**

1034 **NUVIGIL may cause serious side effects. Call your doctor or get emergency help if**
1035 **you have any of the including:**

- 1036 • **a serious rash or serious allergic reaction. (See, “What is the most important**
1037 **information I should know about NUVIGIL.”)**

- 1038 • **mental (psychiatric) symptoms.** Symptoms include depression, anxiety,
1039 hallucinations, mania, thoughts of suicide or other mental problems.

- 1040 • **heart problems including chest pain**

1041

1042 The most common side effects of NUVIGIL are headache, nausea, dizziness, and trouble
1043 sleeping.

1044

1045 NUVIGIL may cause allergic reactions. If you get a rash, hives or other allergic reaction,
1046 stop taking NUVIGIL and call your doctor right away.

1047

1048 If you have either of the problems listed below or any other serious side effects while
1049 taking NUVIGIL stop taking NUVIGIL and call your doctor or get emergency help:

- 1050 • chest pain.

- 1051 • mental problems.

1052

1053 Some effects of NUVIGIL on the brain are the same as other medicines called
1054 **“stimulants”**. **These effects may lead to** abuse or dependence on NUVIGIL. Before
1055 starting NUVIGIL, tell your doctor if you have ever abused drugs, including other
1056 stimulant medicines.

1057

1058 Tell your doctor if you get any side effect that bothers you or that does not go away while
1059 taking NUVIGIL.

1060

1061 These are not all the side effects of NUVIGIL. For more information, ask your doctor or
1062 pharmacist.

1063

1064 **How should I store NUVIGIL?**

1065 • Store NUVIGIL at room temperature, 68° to 77° F (20° to 25° C).

1066 • Keep NUVIGIL and all medicines out of the reach of children.

1067

1068 **General information about NUVIGIL**

1069 Medicines are sometimes prescribed for conditions that are not listed in patient
1070 information leaflets. Do not use NUVIGIL for a condition for which it was not
1071 prescribed. **Do not give NUVIGIL to other people, even if they have the same**
1072 **symptoms you have. It may harm them and it is against the law.**

1073 This leaflet summarizes the most important information about NUVIGIL. If you would
1074 like more information, talk with your doctor. You can ask your doctor or pharmacist for
1075 information about NUVIGIL that is written for health professionals. For more
1076 information, please call 1-800-896-5855, or go to www.NUVIGIL.com.

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1078 **What are the ingredients in NUVIGIL?**

1079 **Active Ingredient:** armodafinil

1080 **Inactive Ingredients:** croscarmellose sodium, lactose, magnesium stearate,
1081 microcrystalline cellulose, povidone, and pregelatinized starch.

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1083 **Rx Only**

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1085 June 2007

1086 NUVPIIL - 001

1087 Cephalon, Inc. Frazer, PA 19355

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1089 This Patient Information Leaflet has been approved by the U.S. Food and Drug

1090 Administration.

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