

ARMODAFINIL- armodafinil tablet

Mylan Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ARMODAFINIL tablets, for oral use CIV
Initial U.S. Approval: 2007

INDICATIONS AND USAGE

Armodafinil tablets are 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, armodafinil tablets are indicated to treat excessive sleepiness and not as treatment for the underlying obstruction.

DOSAGE AND ADMINISTRATION

The recommended dosage of armodafinil tablets 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, and 250 mg. (3)

CONTRAINDICATIONS

Armodafinil tablets are contraindicated in patients with known hypersensitivity to modafinil or armodafinil. (4)

WARNINGS AND PRECAUTIONS

- Serious Rash, including Stevens-Johnson Syndrome: discontinue armodafinil tablets at the first sign of rash, unless the rash is clearly not drug-related. (5.1)
- DRESS/Multi-organ Hypersensitivity Reactions: if suspected, discontinue armodafinil tablets. (5.2)
- Angioedema and Anaphylaxis Reactions: if suspected, discontinue armodafinil tablets. (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 armodafinil tablets if psychiatric symptoms develop. (5.5)
- Known Cardiovascular Disease: consider increased monitoring. (5.7)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 5\%$): headache, nausea, dizziness, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) 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 armodafinil tablets and for one month after discontinuation of armodafinil tablet treatment. (7)
- Cyclosporine: blood concentrations of cyclosporine may be reduced. (7)
- CYP2C19 substrates, such as omeprazole, phenytoin, and diazepam: exposure of these medications may be increased. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy: based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Armodafinil tablets are 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, armodafinil tablets are 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 armodafinil tablets for excessive sleepiness.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Obstructive Sleep Apnea (OSA) and Narcolepsy

The recommended dosage of armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets 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

Armodafinil Tablets are available containing 50 mg, 150 mg or 250 mg of armodafinil.

- The 50 mg tablets are white to off-white, round, unscored tablets debossed with **M** on one side of the tablet and **A31** on the other side.
- The 150 mg tablets are white to off-white, round, unscored tablets debossed with **M** on one side of the tablet and **A32** on the other side.
- The 250 mg tablets are white to off-white, capsule shaped, unscored tablets debossed with **M** on one side of the tablet and **A33** on the other side.

4 CONTRAINDICATIONS

Armodafinil tablets are contraindicated in patients with known hypersensitivity to modafinil or armodafinil or their 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 armodafinil tablets or modafinil (the racemic mixture of S- and R-enantiomers).

Armodafinil tablets have not been studied in pediatric patients in any setting and are 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 armodafinil tablets 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 armodafinil tablets.

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 armodafinil tablets. 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 armodafinil tablets, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, armodafinil tablets 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 armodafinil tablets. 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 armodafinil tablet 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, armodafinil tablets 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 armodafinil tablets. 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 armodafinil tablets should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking armodafinil tablets, 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 armodafinil tablets, anxiety, agitation, nervousness, and irritability were reasons for treatment

discontinuation more often in patients on armodafinil tablets compared to placebo (armodafinil tablets 1.2% and placebo 0.3%). Depression was also a reason for treatment discontinuation more often in patients on armodafinil tablets compared to placebo (armodafinil tablets 0.6% and placebo 0.2%). Cases of suicidal ideation were observed in clinical trials.

Caution should be exercised when armodafinil tablets are given to patients with a history of psychosis, depression, or mania. If psychiatric symptoms develop in association with armodafinil tablet administration, consider discontinuing armodafinil tablets.

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

Postmarketing adverse reactions associated with the use of armodafinil tablets, 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 armodafinil tablet 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 armodafinil tablets have 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 armodafinil tablet 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 armodafinil 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 armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets. Caution should be exercised when prescribing armodafinil tablets 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.

Armodafinil tablets have 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 ($\geq 5\%$) associated with the use of armodafinil tablets 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 armodafinil tablet-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 Armodafinil Tablets (150 mg and 250 mg)

	Armodafinil Tablets (%) 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 $\geq 1\%$ of armodafinil tablet-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 armodafinil tablets 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

	Armodafinil Tablets 250 mg (%) N = 198	Armodafinil Tablets 150 mg (%) N = 447	Armodafinil Tablets 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 armodafinil tablets 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 armodafinil tablets, 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 armodafinil tablets. 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 Armodafinil Tablets 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 armodafinil tablets 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 armodafinil tablets [see *Clinical Pharmacology (12.3)*].

The effectiveness of steroidal contraceptives may be reduced when used with armodafinil tablets 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 armodafinil tablets and for one month after discontinuation of armodafinil tablet treatment.

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

armodafinil tablets.

Effects of Armodafinil Tablets on CYP2C19 Substrates: Elimination of drugs that are substrates for CYP2C19 (e.g., phenytoin, diazepam, propranolol, omeprazole, and clomipramine) may be prolonged by armodafinil tablets 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 armodafinil tablets.

Warfarin: More frequent monitoring of prothrombin times/INR should be considered whenever armodafinil tablets are coadministered with warfarin [see *Clinical Pharmacology* (12.3)].

Monoamine Oxidase (MAO) Inhibitors: Caution should be used when concomitantly administering MAO inhibitors and armodafinil tablets.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 armodafinil tablets (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 armodafinil tablets. 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 armodafinil tablets.

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 armodafinil tablets. 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 armodafinil tablets 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 armodafinil tablets and for one month after discontinuation of armodafinil tablet 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 armodafinil tablets 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

Armodafinil tablets contain armodafinil, a Schedule IV controlled substance.

9.2 Abuse

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

Abuse of armodafinil, the active ingredient of armodafinil tablets, poses a risk of overdose similar to that seen for modafinil, which may lead to tachycardia, insomnia, agitation, dizziness, anxiety, nausea, headache, dystonia, tremor, chest pain, hypertension, seizures, 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.

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 armodafinil tablets. 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 armodafinil tablets have been reported during the postmarketing period.

10 OVERDOSAGE

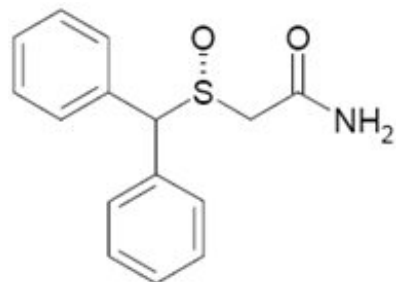
Fatal overdoses involving modafinil alone or involving armodafinil tablets or modafinil in combination with other drugs have been reported in the postmarketing setting. Symptoms most often accompanying armodafinil tablet or modafinil overdose, alone or in combination with other drugs, have included anxiety, 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 an armodafinil tablet overdose. Such overdoses should be managed with primarily supportive care, including cardiovascular monitoring.

11 DESCRIPTION

Armodafinil tablets are 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 R-(-)-2-[(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 powder that is slightly soluble in water, sparingly soluble in acetone, and soluble in methanol.

Armodafinil tablets contain 50, 150, or 250 mg of armodafinil and the following inactive

ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and povidone.

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 α 1-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 armodafinil tablets 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 armodafinil tablets 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

Armodafinil tablets are 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 armodafinil 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 armodafinil tablets.

Distribution

Armodafinil 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 armodafinil tablets with highly protein-bound drugs is considered to be minimal.

Elimination

After oral administration of armodafinil tablets, armodafinil exhibits an apparent monoexponential decline from the peak plasma concentration. The apparent terminal $t_{1/2}$ is approximately 15 hours. The oral clearance of armodafinil 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 armodafinil 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 armodafinil tablets 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 Armodafinil Tablets 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 armodafinil tablets 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 armodafinil tablets [see *Drug Interactions (7)*].

In a separate clinical study, concomitant administration of armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets with quetiapine reduced the systemic exposure of quetiapine.

Data specific to armodafinil 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 armodafinil tablets.

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 armodafinil 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 armodafinil 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 armodafinil tablets.

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 armodafinil tablets (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 armodafinil tablets.

14 CLINICAL STUDIES

14.1 Obstructive Sleep Apnea (OSA)

The effectiveness of armodafinil tablets in improving wakefulness in patients with excessive sleepiness associated with OSA was established in two 12-week, multi-center, placebo-controlled, parallel-group, double-blind clinical studies of outpatients who met the criteria for OSA. The criteria include either: 1) excessive sleepiness or insomnia, plus frequent episodes of impaired breathing during sleep, and associated features such as loud snoring, morning headaches or dry mouth upon awakening; or 2) excessive sleepiness or insomnia; and polysomnography demonstrating one of the following: more than five obstructive apneas, each greater than 10 seconds in duration, per hour of sleep; and one or more of the following: frequent arousals from sleep associated with the apneas, bradycardia, or arterial oxygen desaturation in 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 $\geq 70\%$ 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 armodafinil tablets 150 mg/day, armodafinil tablets 250 mg/day or matching placebo. Patients treated with armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets 150 mg/day or placebo. Patients treated with armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets in either study.

14.2 Narcolepsy

The effectiveness of armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets 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

armodafinil tablets.

14.3 Shift Work Disorder (SWD)

The effectiveness of armodafinil tablets 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 armodafinil tablets 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 \leq 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 armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets.

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

Disorder	Measure	Armodafinil Tablets 150 mg*		Armodafinil Tablets 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	Armodafinil Tablets 150 mg*	Armodafinil Tablets 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

Armodafinil Tablets are available containing 50 mg, 150 mg or 250 mg of armodafinil.

The 50 mg tablets are white to off-white, round, unscored tablets debossed with **M** on one side of the tablet and **A31** on the other side. They are available as follows:

NDC 0378-3431-93
bottles of 30 tablets

The 150 mg tablets are white to off-white, round, unscored tablets debossed with **M** on one side of the tablet and **A32** on the other side. They are available as follows:

NDC 0378-3432-93
bottles of 30 tablets

The 250 mg tablets are white to off-white, capsule shaped, unscored tablets debossed with **M** on one side of the tablet and **A33** on the other side. They are available as follows:

NDC 0378-3433-93
bottles of 30 tablets

16.2 Storage

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Medication Guide with each prescription.

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 armodafinil tablets and consult with their healthcare provider immediately if a skin reaction such as

rash, mouth sores, blisters, or peeling skin occurs during treatment with armodafinil tablets [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 armodafinil tablets. Instruct them to discontinue armodafinil tablets and immediately report these symptoms to their healthcare provider [see *Warnings and Precautions (5.3)*].

Wakefulness: Advise patients that treatment with armodafinil tablets 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 armodafinil tablets has been shown to produce levels of wakefulness that permit such activities. Advise patients that armodafinil tablets are 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 armodafinil tablets and contact their physician right away if they experience depression, anxiety, or signs of psychosis or mania.

Females of Reproductive Potential: Caution females regarding the potential increased risk of pregnancy when using hormonal contraceptives (including depot or implantable contraceptives) with armodafinil tablets 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 armodafinil tablets and for one month after discontinuation of armodafinil tablets.

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 armodafinil tablets and other drugs.

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

Medication Guide

Armodafinil Tablets CIV (ar moe daf' i nil)
What is the most important information I should know about armodafinil tablets?

Armodafinil tablets are a federal controlled substance (C-IV) because they can be abused or lead to dependence. Keep armodafinil tablets in a safe place to prevent misuse and abuse. Selling or giving away armodafinil tablets 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.

Armodafinil tablets 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 armodafinil tablets 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 armodafinil tablets, stopping the medicine may not keep the rash from becoming life-threatening or causing you to be permanently disabled or disfigured.

Armodafinil tablets are not approved for use in children for any medical condition.

It is not known if armodafinil tablets are safe and effective in children under the age of 18.

What are armodafinil tablets?

Armodafinil tablets are 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). Armodafinil tablets are used with other medical treatments for this sleep disorder. Armodafinil tablets do 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)

Armodafinil tablets will not cure these sleep disorders. Armodafinil tablets may help the sleepiness caused by these conditions, but they may not stop all your sleepiness. Armodafinil tablets do not take the place of getting enough sleep. Follow your doctor's advice about good sleep habits and using other treatments.

Do not take armodafinil tablets if you:

- are allergic to any of their ingredients. See the end of this Medication Guide for a complete list of ingredients in armodafinil tablets.
- have had a rash or allergic reaction to either armodafinil (armodafinil tablets) or modafinil (PROVIGIL[®]). These medicines are very similar.

Before you take armodafinil tablets, 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 armodafinil tablets.
- 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 armodafinil tablets will harm your unborn baby.
- are breastfeeding. It is not known if armodafinil passes into your milk. Talk to your doctor about the best way to feed your baby if you take armodafinil tablets.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Armodafinil tablets and many other medicines can interact with each other, sometimes causing side effects. Armodafinil tablets may affect the way other medicines work, and other medicines may affect how armodafinil tablets work. Your dose of armodafinil tablets 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 armodafinil tablets. Women who use one of these methods of birth control may have a higher chance for getting pregnant while taking armodafinil tablets, and for 1 month after stopping armodafinil tablets. You should use effective birth control while taking armodafinil tablets and for 1 month after your final dose. Talk to your doctor about birth control choices that are right for you while taking armodafinil tablets.

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 armodafinil tablets and other medicines together. Do not start any new medicines with armodafinil tablets unless your doctor has told you it is okay.

How should I take armodafinil tablets?

- Take armodafinil tablets exactly as prescribed by your doctor. Your doctor will prescribe the dose of armodafinil tablets that is right for you. Do not change your dose of armodafinil tablets without talking to your doctor.
- Your doctor will tell you the right time of day to take armodafinil tablets.
 - People with narcolepsy or OSA usually take armodafinil tablets one time each day in the morning.
 - People with SWD usually take armodafinil tablets about 1 hour before their work shift.
- Do not change the time of day you take armodafinil tablets unless you have talked to your doctor. If you take armodafinil tablets too close to your bedtime, you may find it harder to go to sleep.
- You can take armodafinil tablets with or without food.
- If you take more than your prescribed dose or if you take an overdose of armodafinil tablets, call your doctor or poison control center right away.

Symptoms of an overdose of armodafinil tablets may include:

- | | |
|-----------------------|--------------------------------|
| • trouble sleeping | • restlessness |
| • confusion | • feeling disoriented |
| • feeling excited | • hearing, seeing, feeling, or |
| • nausea and diarrhea | sensing things that are |
| • chest pain | not really there |
| • anxiety | (hallucinations) |

- a fast or slow heartbeat
- increased blood pressure
- shortness of breath

What should I avoid while taking armodafinil tablets?

- Do not drive a car or do other dangerous activities until you know how armodafinil tablets affect 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 armodafinil tablets.

What are the possible side effects of armodafinil tablets?

Armodafinil tablets may cause serious side effects.

Stop taking armodafinil tablets 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 armodafinil tablets?”)
- **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.

The most common side effects of armodafinil tablets include:

- headache
- dizziness
- nausea
- trouble sleeping

These are not all the possible side effects of armodafinil tablets.

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 armodafinil tablets?

- Store armodafinil tablets at room temperature between 20° to 25°C (68° to 77°F).
- **Keep armodafinil tablets and all medicines out of the reach of children.**

General information about the safe and effective use of armodafinil tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use armodafinil tablets for a condition for which they were not prescribed. Do not give armodafinil tablets to other people, even if they have the same symptoms that you have. They may harm them and it is against the law.

You can ask your pharmacist or healthcare provider for information about armodafinil tablets that is written for health professionals.

What are the ingredients in armodafinil tablets?

Active ingredient: armodafinil

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and povidone.

Manufactured for: Mylan Pharmaceuticals Inc., Morgantown, WV 26505 U.S.A.

Manufactured by: Mylan Laboratories Limited, Hyderabad – 500 096, India

The brands listed are trademarks of their respective owners.

For more information, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX).

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

Manufactured for:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Manufactured by:

Mylan Laboratories Limited
Hyderabad — 500 096, India

75065951

Revised: 9/2018

MX:ARDFL:R7

PRINCIPAL DISPLAY PANEL - 50 mg

NDC 0378-3431-93

**Armodafinil
Tablets CIV
50 mg**

**PHARMACIST: Dispense the accompanying
Medication Guide to each patient.**

Rx only 30 Tablets

Each tablet contains:

Armodafinil 50 mg

Usual Dosage: See accompanying
prescribing information.

**Keep this and all medication out of
the reach of children.**

**Store at 20° to 25°C (68° to 77°F). [See
USP Controlled Room Temperature.]**

Manufactured for:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

Mylan.com

RMX3431H2

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Each tablet contains:
 Armodafinil 50 mg
Usual Dosage: See accompanying prescribing information.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
 Manufactured for:
 Mylan Pharmaceuticals Inc.
 Morgantown, WV 26505 U.S.A.
 Made in India

NDC 0378-3431-93

Armodafinil
Tablets CIV

50 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Mylan[®]

Rx only 30 Tablets

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed.
 Code No.: MH/DRUGS/25/NKD/89

(42 x 16 mm)
 Varnish Free area for Variable Data Coding online

75104303

Prompt "LOT" & "EXP" will be printed along with Variable Data online Coding (see e.g. below)

LOT 0000000
 EXP YYYY-MM
 *SNO 00000000000
 *GTIN 00000000000000
 *(wherever is applicable)

PRINCIPAL DISPLAY PANEL - 150 mg

NDC 0378-3432-93

Armodafinil
Tablets CIV
150 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only 30 Tablets

Each tablet contains:
 Armodafinil 150 mg

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Manufactured for:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

Mylan.com

RMX3432H2

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Each tablet contains:
Armodafinil 150 mg
Usual Dosage: See accompanying prescribing information.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in India

NDC 0378-3432-93

Armodafinil
Tablets CIV
150 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Mylan®
Rx only 30 Tablets

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed.
Code No.: MH/DRUGS/25/NKD/89

(42 x 16 mm)
Varnish Free area for Variable Data Coding online

Prompt "LOT" & "EXP" will be printed along with Variable Data online Coding (see e.g. below)

LOT 0000000
EXP YYYY-MM
*SNO 0000000000
*GTIN 0000000000000
*(wherever is applicable)

PRINCIPAL DISPLAY PANEL - 250 mg

NDC 0378-3433-93

Armodafinil
Tablets CIV
250 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only 30 Tablets

Each tablet contains:

Armodafinil 250 mg

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Manufactured for:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

Mylan.com

RMX3433H2

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Each tablet contains:
 Armodafinil 250 mg
Usual Dosage: See accompanying prescribing information.
Keep this and all medication out of the reach of children.
 Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
 Manufactured for:
Mylan Pharmaceuticals Inc.
 Morgantown, WV 26505 U.S.A.
 Made in India

NDC 0378-3433-93

Armodafinil
Tablets 
250 mg 

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Mylan
 Mylan.com

RIMX3433H2

Rx only **30 Tablets**


 N 3 0378-3433-93 6
 75104305 

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
 Keep container tightly closed.
 Code No.: MH/DRUGS/25/NKD/89

*(42 x 16 mm)
 Varnish Free area for
 Variable Data Coding online*

Prompt "LOT" & "EXP" will be printed along with Variable Data online Coding (see e.g. below)

LOT 0000000 
 EXP YYYY-MM
 *SNO 00000000000
 *GTIN 00000000000000
 *(wherever is applicable)

ARMODAFINIL			
armodafinil tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0378-3431
Route of Administration	ORAL	DEA Schedule	CIV
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
ARMODAFINIL (UNII: V63XWA605I) (ARMODAFINIL - UNII:V63XWA605I)		ARMODAFINIL	50 mg
Inactive Ingredients			
Ingredient Name			Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)			
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)			
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)			
MAGNESIUM STEARATE (UNII: 70097M6I30)			
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)			

Product Characteristics

Color	WHITE (white to off-white)	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	M;A31
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-3431-93	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/01/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200043	06/01/2016	

ARMODAFINIL

armodafinil tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0378-3432
Route of Administration	ORAL	DEA Schedule	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ARMODAFINIL (UNII: V63XWA605I) (ARMODAFINIL - UNII:V63XWA605I)	ARMODAFINIL	150 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics

Color	WHITE (white to off-white)	Score	no score
Shape	ROUND	Size	10mm

Flavor		Imprint Code	M;A32	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-3432-93	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/01/2016	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA200043	06/01/2016		

ARMODAFINIL

armodafinil tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0378-3433
Route of Administration	ORAL	DEA Schedule	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ARMODAFINIL (UNII: V63XWA605I) (ARMODAFINIL - UNII:V63XWA605I)	ARMODAFINIL	250 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics

Color	WHITE (white to off-white)	Score	no score
Shape	OVAL (capsule shaped)	Size	15mm
Flavor		Imprint Code	M;A33
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-3433-93	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/01/2016	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA200043	06/01/2016		

Labeler - Mylan Pharmaceuticals Inc. (059295980)

Revised: 9/2018

Mylan Pharmaceuticals Inc.