For the use of a Psychiatrist only.

Prescribing Information

Armodafinil Tablets

Waklert®

Dosage Form:
Tablet

Composition:
Each Uncoated Tablet of **Waklert® 50** Contains:
Armodafinil IP 50 mg

Each Uncoated Tablet of **Waklert® 150** Contains:
Armodafinil IP 150 mg

Each Uncoated Tablet of **Waklert® 250** Contains:
Armodafinil IP 250 mg

PEXP10038C

Indications:
Waklert® is indicated to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome (OSAHS), narcolepsy and shift work sleep disorder.

In OSAHS, **Waklert®** is indicated as an adjunct to standard treatment(s) 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 **Waklert®**. If **Waklert®** is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

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

The effectiveness of armodafinil tablets in long term use (greater than 12 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to prescribe armodafinil tablets for an extended time in patients should periodically reevaluate long term usefulness for the individual patient.

Dosage and Administration
Obstructive sleep apnea/hypopnea syndrome (OSAHS) and narcolepsy: The recommended dose of **Waklert®** for patients with OSAHS or narcolepsy is 150 mg or 250 mg given as a single dose in the morning. In patients with OSAHS, doses up to 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 150 mg/day dose.

Shift work sleep disorder (SWSD): The recommended dose of **Waklert®** for patients with SWSD is 150 mg given daily approximately 1 hour prior to the start of their work shift.

Dosage adjustment should be considered for concomitant medications that are substrates for CYP3A4/5, such as steroidal contraceptives, triazolam, and cyclosporine.

Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, and phenytoin may have prolonged elimination upon coadministration with **Waklert®** and may require dosage reduction and monitoring for toxicity.

Elderly: Safety and effectiveness of armodafinil tablets in individuals above 65 years of age have not been established. 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 in this population.

Pediatric use: Safety and effectiveness of armodafinil use in individuals below 17 years of age have not been established. Serious rash has been seen in pediatric patients receiving modafinil.

Hepatic impairment: In patients with severe hepatic impairment, with or without cirrhosis, armodafinil tablets should be administered at a reduced dose.

Renal impairment: There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment.

Contra-indications:
In patients with known hypersensitivity to modafinil and armodafinil or its inactive ingredients.

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

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

In clinical trials of modafinil (the racemate), 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 multiorgan hypersensitivity reaction. 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. No serious skin rashes have been reported in adult clinical trials (0 per 4,264) of modafinil. Rare cases of serious or life-threatening rash, including SJS, Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported in adults and children in worldwide post-marketing experience. The reporting rate of TEN and SJS associated with modafinil use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate. Estimates of the background incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years.

No serious skin rashes have been reported in adult clinical trials of armodafinil. However, because armodafinil is the R isomer of racemic modafinil, a similar risk of serious rash with armodafinil cannot be ruled out.

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

Although benign rashes also occur with armodafinil, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, armodafinil should ordinarily be discontinued at the first sign of rash, 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.

One serious case of angioedema and one case of hypersensitivity (with rash, dysphagia, and bronchospasm), were observed among 1,595 patients treated with armodafinil. 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).

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. A similar risk of multi-organ hypersensitivity reactions with armodafinil cannot be ruled out.

Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalization or be lifethreatening. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions associated with modafinil. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included myocarditis, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia.

Because multi-organ hypersensitivity is variable in its expression, other organ system symptoms and signs, not noted here, may occur.

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 multiorgan hypersensitivity would indicate this to be a possibility.

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.

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

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

In the controlled trial armodafinil tablets database, 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%). In the armodafinil tablets controlled studies, 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%). Two cases of suicide ideation were observed in clinical trials. Caution should be exercised when armodafinil tablets is given to patients with a history of psychosis, depression, or mania. If psychiatric symptoms develop in association with armodafinil tablets administration, consider discontinuing armodafinil tablets.

Armodafinil tablets should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of either narcolepsy, OSAHS, and/or SWSD has been made in accordance with ICSD or DSM diagnostic criteria. Such an evaluation usually consists of a complete history and physical examination, and it may be supplemented with testing in a laboratory setting. Some patients may have more than one sleep disorder contributing to their excessive sleepiness (e.g., OSAHS and SWSD coincident in the same patient).

In OSAHS, armodafinil tablets is indicated as an adjunct to standard treatment(s) 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. If armodafinil tablets is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary. There was a slight trend for reduced CPAP use over time (mean reduction of 18 minutes for patients treated with armodafinil tablets and a 6 minute reduction for placebo treated patients from a mean baseline use of 6.9 hours per night) in armodafinil tablets trials.

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

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

In clinical studies of modafinil, signs and symptoms 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. Signs 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 symptoms occurs, consider cardiac evaluation.

Blood pressure monitoring in short term (≤ 3 months) controlled trials showed only 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%). Increased monitoring of blood pressure may be appropriate in patients on armodafinil tablets.

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 treated with armodafinil tablets and for one month after discontinuation of armodafinil tablets treatment.

The 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 these drugs are used concomitantly.

In patients with severe hepatic impairment, with or without cirrhosis, armodafinil tablets should be administered at a reduced dose.

There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment.

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 in this population.

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

Patients should be advised 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 and other drugs.

Patients should be advised that the use of armodafinil tablet in combination with alcohol has not been studied. Patients should be advised that it is prudent to avoid alcohol while taking armodafinil tablets.

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

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 subjects, however, had GGT or AP elevations outside of the normal range. No differences were apparent in alanine aminotransferase, aspartate aminotransferase, 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.

No pattern of ECG abnormalities could be attributed to armodafinil administration in placebo controlled clinical trials.

Although the abuse potential of armodafinil has not been specifically studied, its abuse potential is likely to be similar to that of modafinil. 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).

Pregnancy & Lactation

Armodafinil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be cautioned regarding the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with armodafinil tablets and for one month after discontinuation of therapy.

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

It is not known whether armodafinil or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when armodafinil tablets are administered to a nursing woman.

Drug Interactions:

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 levels of armodafinil.

In vitro data demonstrated that armodafinil shows a weak inductive response for CYP1A2 and possibly CYP3A activities in a concentration related manner and demonstrated that CYP2C19 activity is reversibly inhibited by armodafinil. However, the effect on CYP1A2 activity was not observed clinically in an interaction study performed with caffeine.

Chronic administration of armodafinil tablets resulted in moderate induction of CYP3A activity. Hence, the effectiveness of drugs that are substrates for CYP3A enzymes (e.g., cyclosporine, ethinyl estradiol, midazolam and triazolam) may be reduced after initiation of concurrent treatment with armodafinil tablets. A 32% reduction in systemic exposure of oral midazolam was seen upon concomitant administration of armodafinil with midazolam. Dose adjustment may be required.

Such effects (reduced concentrations) were also seen upon concomitant administration of modafinil with cyclosporine, ethinyl estradiol, and triazolam.

Administration of armodafinil tablet resulted in moderate inhibition of CYP2C19 activity. Hence, dosage reduction may be required for some drugs that are substrates for CYP2C19 (e.g. phenytoin, diazepam, and propranolol, omeprazole and clomipramine) when used concurrently with armodafinil tablet. A 40% increase in exposure was seen upon concomitant administration of armodafinil with omeprazole.

Data specific to armodafinil drug-drug interaction potential with CNS active drugs are not available. However, the following available drug-drug interaction information on modafinil should be applicable to armodafinil.

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. Therefore, caution should be used when concomitantly administering MAO inhibitors and armodafinil tablets.

Data specific to armodafinil drug-drug interaction potential for additional other drugs are not available. However, the available drug-drug interaction information on modafinil should be applicable to armodafinil. 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, a pharmacodynamic interaction cannot be ruled out. Therefore, more frequent monitoring of prothrombin times/INR should be considered whenever armodafinil tablet is coadministered with warfarin.

Side effects:

The most common adverse events reported by ≥5% of patients on armodafinil treatment include headache, nausea, dizziness and insomnia.

The adverse events observed with armodafinil in > 1% of patients were palpitations, diarrhea, dry mouth, dyspepsia, upper abdominal pain, constipation, vomiting, loose stools, fatigue, thirst, influenza like illness, pain, pyrexia, seasonal allergy, increased gamma-glutamyltransferase, increased heart rate, anorexia, decreased appetite, disturbance in attention, tremor, migraine, paraesthesia, anxiety, depression, agitation, nervousness, depressed mood, polyuria, dyspnea, rash, contact dermatitis, hyperhydrosis etc.

Overdosage:

There were no overdoses reported in the clinical studies of armodafinil tablets.

Symptoms of armodafinil tablets overdose are likely to be similar to those of modafinil. Overdose in modafinil clinical trials included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. From post-marketing experience with modafinil, there have been no reports of fatal overdoses involving modafinil alone (doses up to 12 grams). Overdoses involving multiple drugs, including modafinil, have resulted in fatal outcomes. Symptoms most often accompanying modafinil overdose, alone or in combination with other drugs have included; 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 armodafinil tablet overdose. Such overdoses should be managed with primarily supportive care, including cardiovascular monitoring. If there are no contraindications, induced emesis or gastric lavage should be considered. There are no data to suggest the utility of dialysis or urinary acidification or alkalinization in enhancing drug elimination.

Clinical Pharmacology:

Armodafinil is a wakefulness promoting agent.

Mechanism of Action

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

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

Armodafinil is not a direct- or indirect-acting dopamine receptor agonist. However, in vitro, both armodafinil and modafinil bind 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.

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. 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.

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.

Pharmacokinetics

The active component of armodafinil tablets is armodafinil, which is the longer-lived enantiomer of modafinil. Armodafinil tablets 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 tablets was reached within 7 days of dosing. At steady state, the systemic exposure for armodafinil tablets is 1.8 times the exposure observed after a single dose. The concentration-time profiles of the pure R-enantiomer following administration of 50 mg armodafinil tablets or 100 mg modafinil are nearly superimposable.

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

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.

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).

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).

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 tablets is approximately 33 mL/min.

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.

In vitro data demonstrated that armodafinil shows a weak inductive response for 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.

Chronic administration of armodafinil tablets at 250 mg reduced the systemic exposure to midazolam by 32% and 17% after single oral (5 mg) and intravenous (2 mg) doses, respectively, suggesting that administration of armodafinil tablets moderately induces CYP3A activity. Drugs that are substrates for CYP3A4/5, such as cyclosporine, may require dosage adjustment.

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

Coadministration of a single 400 mg dose of armodafinil tablets with omeprazole (40 mg) increased systemic exposure to omeprazole by approximately 40%, indicating that armodafinil moderately inhibits CYP2C19 activity. Drugs that are substrates for CYP2C19 may require dosage reduction.

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

A slight decrease (~20%) in the oral clearance (CL/F) of modafinil was observed in a single dose study at 200 mg in 12 subjects with a mean age of 63 years (range 53 -72 years), but the change was considered not likely to be clinically significant. In a multiple dose study (300 mg/day) in 12 patients with a mean age of 82 years (range 67 - 87 years), the mean levels of modafinil in plasma were approximately two times those historically obtained in matched younger subjects. Due to potential effects from the multiple concomitant medications with which most of the patients were being treated, the apparent difference in modafinil pharmacokinetics may not be attributable solely to the effects of aging. However, the results suggest that the clearance of modafinil may be reduced in the elderly.

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 was increased 9-fold.

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. The dose of armodafinil tablets should be reduced in patients with severe hepatic impairment.

Incompatibilities:

None reported.

Storage & Handling:

Store at room temperature, protected from light and moisture. Keep out of reach of children.

Expiry Date:

Refer product label for expiry date. Do not use after expiry date.

Presentation:

Waklert® 50/Waklert® 150/Waklert® 250 is available in strips of 10 tablets.

® Registered Trade Mark

For further details, please write to:

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