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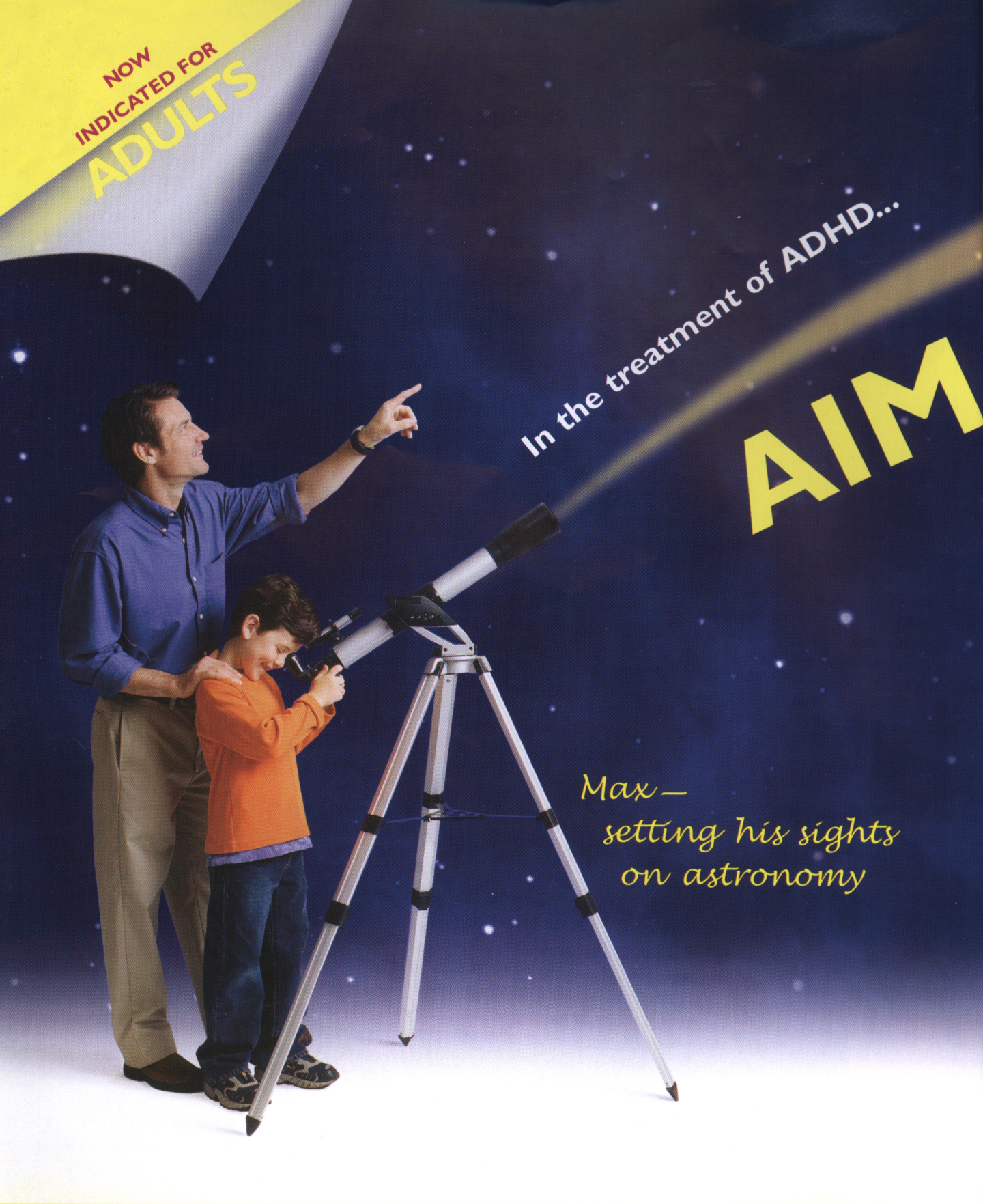

The most common adverse events in pediatric trials included loss of appetite, insomnia, abdominal pain, and emotional lability. The most common adverse events in the adult trial included dry mouth, loss of appetite, insomnia, headache, and weight loss.

The effectiveness of ADDERALL XR for long-term use has not been systematically evaluated in controlled trials. As with other psychostimulants indicated for ADHD, there is a potential for exacerbating motor and phonic tics and Tourette's syndrome. A side effect seen with the amphetamine class is psychosis. Caution also should be exercised in patients with a history of psychosis.

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References: 1. Ambrosini PJ, Lopez FA, Chandler MC, et al. Safety and efficacy of ADDERALL XR in pediatric ADHD: results of an open-label community assessment trial. **Poster presented at: 14th Annual CHADD International Conference; October 17, 2002; Miami Beach, Fla. 2.** Spencer T, Biederman J, Wilens T, et al. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *J Am Acad Child Adolesc Psychiatry.* **1996;35:409-432. 3.** Lopez FA, Ambrosini PJ, Chandler MC, et al. ADDERALL XR in pediatric ADHD: quality of life measures from an open-label community assessment trial. Poster presented at: 14th Annual CHADD International Conference; October 17, 2002; Miami Beach, Fla. **4.** Lopez FA, Chandler MC, Biederman J, et al. Long-term Adderall XR treatment improves quality of life in ADHD children. Poster presented at: 156th Annual Meeting of the American Psychiatric Association; May 21, 2003; San Francisco, Calif.

BRIEF SUMMARY: Consult the full prescribing information for complete product information.

ADDERALL XR® CAPSULES **CII Rx Only**

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

INDICATIONS

ADDERALL XR® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of ADDERALL XR® in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, and one controlled trial in adults who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY), along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Psychosis: Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

Long-Term Suppression of Growth: Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR® generally should not be used in children or adults with structural cardiac abnormalities.

PRECAUTIONS

General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR®, especially patients with hypertension.

Tics: Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Drug Interactions: *Acidifying agents*—Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) lower absorption of amphetamines. *Urinary acidifying agents*—These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines. *Adrenergic blockers*—Adrenergic blockers are inhibited by amphetamines. *Alkalinizing agents*—Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Co-administration of ADDERALL XR® and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines. *Antidepressants, tricyclic*—Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated. *MAO inhibitors*—MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results. *Antihistamines*—Amphetamines may counteract the sedative effect of antihistamines. *Antihypertensives*—Amphetamines may antagonize the hypotensive effects of antihypertensives. *Chlorpromazine*—Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning. *Ethosuximide*—Amphetamines may delay intestinal absorption of ethosuximide. *Haloperidol*—Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines. *Lithium carbonate*—The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate. *Meperidine*—Amphetamines potentiate the analgesic effect of meperidine. *Methenamine therapy*—Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy. *Norepinephrine*—Amphetamines enhance the adrenergic effect of norepinephrine. *Phenobarbital*—Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action. *Phenytoin*—Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action. *Propoxyphene*—In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur. *Veratrum alkaloids*—Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis and Impairment of Fertility: No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m² body surface area basis.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release) (d- to l- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m² body surface area basis).

Pregnancy: Pregnancy Category C. Amphetamine, in the enantiomer ratio present in ADDERALL® (d- to l- ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m² body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times that of a human dose of 30 mg/day [child] on a mg/m² basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function. There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Usage in Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use: ADDERALL XR® is indicated for use in children 6 years of age and older.

Use in Children Under Six Years of Age: Effects of ADDERALL XR® in 3-5 year olds have not been studied. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age.

Geriatric Use: ADDERALL XR® has not been studied in the geriatric population.

ADVERSE EVENTS

The premarketing development program for ADDERALL XR® included exposures in a total of 965 participants in clinical trials (635 pediatric patients, 248 adult patients, 82 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N=40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

Adverse events associated with discontinuation of treatment: In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of ADDERALL XR® treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of ADDERALL XR® in controlled and uncontrolled, multiple-dose clinical trials of pediatric patients (N=595) are presented below. Over half of these patients were exposed to ADDERALL XR® for 12 months or more.

Adverse event	% of pediatric patients discontinuing (n=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight loss	1.2
Emotional lability	1.0
Depression	0.7

In one placebo-controlled 4-week study among adults with ADHD, patients who discontinued treatment due to adverse events among ADDERALL XR®-treated patients (N=191) were 3.1% (n=6) for nervousness including anxiety and irritability, 2.6% (n=5) for insomnia, 1% (n=2) each for headache, palpitation, and somnolence; and, 0.5% (n=1) each for ALT increase, agitation, chest pain, cocaine craving, elevated blood pressure, and weight loss.

Adverse events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adults treated with ADDERALL XR® or placebo are presented in the tables below.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1 Adverse Events Reported by More Than 1% of Pediatric Patients Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 584 Patient Clinical Study

Body System	Preferred Term	ADDERALL XR® (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Liability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	Weight Loss	4%	0%

Table 2 Adverse Events Reported by 5% or More of Adults Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR® (n=191)	Placebo (n=64)
General	Asthenia	6%	5%
	Headache	26%	13%
Digestive System	Loss of Appetite	33%	3%
	Diarrhea	6%	0%
	Dry Mouth	35%	5%
	Nausea	8%	3%
Nervous System	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Insomnia	27%	13%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%
Urogenital System	Urinary Tract Infection	5%	0%

Note: The following events did not meet the criterion for inclusion in Table 2 but were reported by 2% to 4% of adult patients receiving ADDERALL XR® with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder, emotional lability, libido decreased, somnolence, speech disorder, palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.

*included doses up to 60 mg.

The following adverse reactions have been associated with amphetamine use: Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke. Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects. Allergic: Urticaria. Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

ADDERALL XR® is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSAGE

Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses. Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment: Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

The prolonged release of mixed amphetamine salts from ADDERALL XR® should be considered when treating patients with overdose. Dispense in a tight, light-resistant container as defined in the USP. Store at 25° C (77° F). Excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature].

Manufactured for: **Shire US Inc.,** Newport, KY 41071 Made in USA For more information call 1-800-828-2088, or visit www.adderallxr.com. ADDERALL® and ADDERALL XR® are registered in the US Patent and Trademark Office. Copyright ©2004 Shire US Inc.

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ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR® EXTENDED RELEASE CAPSULES

BRIEF SUMMARY. See package insert for full prescribing information. **CONTRAINDICATIONS**: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). **WARNINGS: Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Clinical Worsening and Suicide Risk**—Adult and pediatric patients with major depressive disorder (MDD) may experience worsening of depression and/or emergence of suicidal ideation and behavior (suicidality), whether or not taking antidepressants. This risk may persist until significant remission occurs. Although there has long been concern that antidepressants may induce worsening of depression and emergence of suicidality, a causal role has not been established. **Closely observe patients treated with antidepressants for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose increases or decreases.** Consider changing the therapeutic regimen or discontinuing the medication in patients whose MDD is persistently worse or whose emergent suicidality is severe, abrupt in onset, or not part of presenting symptoms. Due to possible comorbidity, when treating patients with other psychiatric and nonpsychiatric disorders, observe the same precautions used when treating MDD patients. Anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adults and pediatrics treated with antidepressants for MDD and other psychiatric and nonpsychiatric indications. Although a causal link between emergence of such symptoms and worsening of depression and/or emergence of suicidal impulses has not been established, consider changing the therapeutic regimen or discontinuing the medication in patients for whom such symptoms are severe, abrupt in onset, or not part of presenting symptoms. **Alert families and caregivers of patients treated with antidepressants for MDD or other psychiatric or nonpsychiatric indications to monitor patients for emergence of agitation, irritability, and other symptoms described above, and emergence of suicidality, and to report such symptoms immediately to health care providers.** Write prescriptions for Effexor XR for the smallest quantity of capsules consistent with good patient management, to reduce risk of overdose. If it is decided to discontinue treatment, medication should be tapered, as rapidly as feasible, but recognizing that abrupt discontinuation can be associated with certain symptoms. Effexor XR is not approved for use in any indications in pediatrics. A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. Prior to initiating antidepressant treatment, adequately screen patients to determine if they are at risk for bipolar disorder; including a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Effexor XR is not approved for use in bipolar depression. **Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. **PRECAUTIONS: General—*Discontinuation of Treatment with Effexor XR*:** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. ***Insomnia and Nervousness***: Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 0.9% of depressed patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0% of SAD patients. ***Changes in Weight: Adult Patients***: In short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In 12-week SAD trials, 3% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. ***Pediatric Patients***: Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% vs. 3.6%; $P<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents >12 years old. ***Changes in Weight: Pediatric Patients***: In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while placebo patients grew an average of 1.0 cm (n=132); $P=0.041$. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). In a 6-month study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents >12 years old. ***Changes in Appetite: Adult Patients***: Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. ***Pediatric Patients***: Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. ***Activation of Mania/Hypomania***: Mania or hypomania has occurred during short-term depression studies. Effexor XR should be used cautiously in patients with a history of mania. ***Hyponatremia***: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. ***Mydriasis***: Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). ***Seizures***: In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. ***Abnormal Bleeding***: Abnormal bleeding (most commonly ecchymosis) has been reported. ***Serum Cholesterol Elevation***: Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. ***Use in Patients With Concomitant Illness***: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Patients and their families should be alert to emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening depression, and suicidal ideation, especially early in antidepressant treatment, and should report such symptoms to the patient's physician if they are severe, abrupt in onset, or not part of presenting symptoms. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities. Tell patients to avoid alcohol while taking Effexor XR and to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations, they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions—*Alcohol***: A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine***: Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam***: A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol***: Venlafaxine decreased total oral-dose clearance of haloperidol resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. ***Lithium***: A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. ***Drugs Highly Bound to Plasma Proteins***: Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. ***Drugs that Inhibit Cytochrome P450 Isoenzymes***: CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. ***Drugs Metabolized by Cytochrome P450 Isoenzymes***: Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. ***Imipramine***: Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. ***Risperidone***: Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4**: Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. ***Indinavir***: In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2**: Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9**: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9 mediated formation of 4-hydroxy-tolbutamide. **CYP2C19**: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). ***MAOIs***: See **CONTRAINDICATIONS** and **WARNINGS**. ***CNS-Active Drugs***: Use caution with concomitant use of venlafaxine and other CNS-active drugs. Based on its mechanism of action and the potential for serotonin syndrome, use caution when co-administering venlafaxine with other drugs affecting the serotonergic neurotransmitter systems, such as triptans, serotonin reuptake inhibitors, or lithium. ***Electroconvulsive Therapy (ECT)***: There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility—*Carcinogenesis***: There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m² basis. ***Mutagenesis***: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. ***Impairment of Fertility***: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis. **Pregnancy—*Teratogenic Effects—Pregnancy Category C***. Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. ***Nonteratogenic Effects***: Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Effectiveness in pediatric patients has not been established (see **WARNINGS-Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS**: ***Associated with Discontinuation of Treatment***—The most common events leading to discontinuation in MDD, GAD, and SAD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, and SAD***—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. ***Vital Sign Changes***: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats per minute in SAD trials. (See **WARNINGS-Sustained Hypertension**). ***Laboratory Changes***: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. ***Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR***—N=5079. "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain: Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, parotitis, periodontitis, proctitis, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalciuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: pathological fracture, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor; Rare: akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, facial paralysis, abnormal gait, Guillain-Barré Syndrome, hyperchlorhydria, hypokinesia, impulse control difficulties, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; Rare: erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, petechial rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, chromatopsia, conjunctival edema, deafness, exophthalmos, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: metrorrhagia, prostatic disorder (prostatitis and enlarged prostate), urination impaired, vaginitis; Infrequent: albuminuria, amenorrhea, cystitis, dysuria, hematuria, leukorrhea, menorrhagia, nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage; Rare: abortion, anuria, breast discharge, breast engorgement, balanitis, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney calculus, kidney pain, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), seizures, vertigo, and death have been reported. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients To or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C011, revised September 2004.

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IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents.

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients.

EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). Adult and pediatric patients taking antidepressants can experience worsening of their depression and/or the emergence of suicidality. **Patients should be observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms. Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Regular BP monitoring is recommended. Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. The most common adverse events reported in EFFEXOR XR short-term placebo-controlled depression, generalized anxiety disorder (GAD), and/or social anxiety disorder trials (incidence ≥10% and ≥2x that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

References: **1.** Data on file, Wyeth Pharmaceuticals Inc. **2.** Effexor XR® (venlafaxine HCl) Extended-Release and Effexor Immediate-Release Prescribing Information, Wyeth Pharmaceuticals Inc.

Please see brief summary of Prescribing Information on adjacent page.

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CNS Spectrums' *editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients, and original research and reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. The journal's goal is to serve as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of central nervous system disease, illness, or trauma.*

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

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SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder and the treatment of schizophrenia. Patients should be periodically reassessed to determine the need for continued treatment.

Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension. A rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported with this class of medications, including SEROQUEL.

There have been reports of diabetes mellitus and hyperglycemia-related adverse events associated with the use of atypical antipsychotics, including SEROQUEL.

The most commonly observed adverse events associated with the use of SEROQUEL in clinical trials were somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, SGPT increase, dyspepsia, and weight gain.

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Please see Brief Summary of Prescribing Information on following page.

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BRIEF SUMMARY of PRESCRIBING INFORMATION

INDICATIONS AND USAGE: Bipolar Mania: SEROQUEL is indicated for the short-term treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex. The efficacy of SEROQUEL in acute bipolar mania was established in two 3-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania. Effectiveness for more than 3 weeks has not been systematically evaluated in clinical trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. **Schizophrenia:** SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients. The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS: Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome. **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS: General: Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (23/2567) of the patients treated with SEROQUEL, compared with 0% (0/607) on placebo and about 0.4% (2/527) on active control drugs. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. **Cataracts: The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology in Prescribing Information). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.** **Seizures:** During clinical trials, seizures occurred in 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. **Hypothyroidism:** Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproate, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels. **Cholesterol and Triglyceride Elevations:** In schizophrenia trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients. **Hyperprolactinemia:** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Priapism:** One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention. **Body Temperature Regulation:** Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose. **Interference with Cognitive and Motor Performance:** Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Nursing:** Patients should be advised not to breast feed if they are taking SEROQUEL. **Concomitant Medication:** As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs. **Alcohol:** Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in avoiding overheating and dehydration. **Laboratory Tests:** No specific laboratory tests are recommended. **Drug Interactions:** The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. SEROQUEL may antagonize the effects of levodopa and dopamine agonists. **The Effect of Other Drugs on Quetiapine: Phenytoin:** Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate). **Divalproex:** Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance. **Thioridazine:** Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A Inhibitors:** Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin). **Fluoxetine, Imipramine, Haloperidol, and Risperidone:** Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine. **Effect of Quetiapine on Other Drugs: Lorazepam:** The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing. **Divalproex:** The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant. **Lithium:** Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. **Antipyrine:** Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis). Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in PRECAUTIONS, General). **Mutagenesis:** The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats. **Impairment of Fertility:** Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of SEROQUEL on labor and delivery in humans is unknown. **Nursing Mothers:** SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed. **Pediatric Use:** The safety and effectiveness of SEROQUEL in pediatric patients have not been established. **Geriatric Use:** Of the approximately 3400 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients.

ADVERSE REACTIONS: The information below is derived from a clinical trial database for SEROQUEL consisting of over 3000 patients. This database includes 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia. Of these approximately 3000 subjects, approximately 2700 (2300 in schizophrenia and 405 in acute bipolar mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 914.3 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Findings Observed in Short-Term, Controlled Trials: Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials: Acute Bipolar Mania:** Overall, discontinuations due to adverse events were 5.7 % for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy. **Schizophrenia:** Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see PRECAUTIONS): Somnolence 0.8% vs 0% for placebo and Hypotension 0.4% vs 0% for placebo. **Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials:** The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied. The following treatment-emergent adverse experiences occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials[1] for the Treatment of Schizophrenia and Acute Bipolar Mania (monotherapy): **Body as a Whole:** Headache, Pain, Asthenia, Abdominal Pain, Back Pain, Fever; **Cardiovascular:** Tachycardia, Postural Hypotension; **Digestive:** Dry Mouth, Constipation, Vomiting, Dyspepsia, Gastroenteritis, Gamma Glutamyl, Transpeptidase Increased; **Metabolic and Nutritional:** Weight Gain, SGPT Increased, SGOT Increased; **Nervous:** Agitation, Somnolence, Dizziness, Anxiety; **Respiratory:** Pharyngitis, Rhinitis; **Skin and Appendages:** Rash; **Special Senses:** Amblyopia [1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%). The following treatment-emergent adverse experiences occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials[1] for the Treatment of Acute Bipolar Mania (Adjunct Therapy): **Body as a Whole:** Headache, Asthenia, Abdominal Pain, Back Pain; **Cardiovascular:** Postural Hypotension; **Digestive:** Dry Mouth, Constipation; **Metabolic and Nutritional:** Weight Gain; **Nervous:** Somnolence, Dizziness, Tremor, Agitation; **Respiratory:** Pharyngitis. [1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%). Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors. **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials: Dose-related Adverse Events:** Spontaneously elicited adverse event data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain. **Extrapyramidal Symptoms:** Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. In six additional placebo-controlled clinical trials trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS. **Vital Signs and Laboratory Studies: Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see PRECAUTIONS). **Weight Gain:** In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see PRECAUTIONS). An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo. **ECG Changes:** Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see PRECAUTIONS). **Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL:** Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for shizophrenia. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Nervous System:** ***Frequent:*** hypertonia, dysarthria; ***Infrequent:*** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma. **Body as a Whole:** ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; ***Rare:*** abdomen enlarged. **Digestive System:** ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. **Cardiovascular System:** ***Frequent:*** palpitation; ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. **Respiratory System:** ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation. **Metabolic and Nutritional System:** ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages System:** ***Frequent:*** sweating; ***Infrequent:*** pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration. **Urogenital System:** ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure. **Special Senses:** ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System:** ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. **Hemic and Lymphatic System:** ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia. **Endocrine System:** ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism. *adjusted for gender **Post Marketing Experience:** Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia. Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Steven Johnson syndrome (SJS).

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: SEROQUEL is not a controlled substance. **Physical and Psychologic dependence:** SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE: Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma or QTc prolongation. **Management of Overdosage:** In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension. There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

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Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, Delaware 19850-5437