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THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE

THE MAZE OF COGNITIVE DYSFUNCTION

FORMAL THOUGHT DISORDER AND SEMANTIC MEMORY IN SCHIZOPHRENIA

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CME Mount Sinai **3**

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PHOTO ESSAY Maze-solving behavior as a tool for the investigation of cognitive disturbance in schizophrenic patients may permit insight into specific impairments in disease-related cognitive processing by testing domains that are preferentially disturbed in schizophrenia.

ARTICLES INSIDE.



On the high wire
of mania...



FOR A SAFE, SMOOTH RETURN TO A MORE NORMAL LIFE...

Smooth, slow release of lithium carbonate for initial or maintenance treatment of mania associated with bipolar disorder

- Smoother blood levels may reduce side effects^{1,2}
 - Helps minimize peak-to-trough variations in serum lithium concentrations
 - Common side effects that may occur during initial therapy include fine hand tremor, polyuria, mild thirst, and transient and mild nausea. These side effects usually subside with continued treatment, temporary reduction of dosage, or cessation.
- Interchangeable with immediate-release lithium preparations on a mg-to-mg basis¹⁻⁴

- Film-coated tablets eliminate metallic taste concerns
- B.I.D. convenience may enhance patient compliance

LITHOBID[®]
Slow-Release Tablets, 300 mg

WARNING: Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy.

Please see brief summary of prescribing information on adjacent page.

Smooth, slow release of lithium carbonate for initial or maintenance treatment of mania associated with bipolar disorder

BRIEF SUMMARY:

The following is a brief summary only. Before prescribing, see complete prescribing information in LITHOBID[®] Slow-Release Tablets product labeling.

WARNING

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy (see DOSAGE AND ADMINISTRATION).

INDICATIONS:

Lithium is indicated in the treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.

Typical symptoms: of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgment, aggressiveness, and possibly hostility. When given to a patient experiencing a manic episode, lithium may produce a normalization of symptomatology within 1 to 3 weeks.

WARNINGS:

Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation, dehydration, sodium depletion, and to patients receiving diuretics, or angiotensin converting enzyme (ACE) inhibitors, since the risk of lithium toxicity is very high in such patients. If the psychiatric indication is life threatening, and if such a patient fails to respond to other measures, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity.

Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus, with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued. Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Morphologic changes have also been seen in manic-depressive patients never exposed to lithium. The relationship between renal function and morphologic changes and their association with lithium therapy have not been established.

Kidney function should be assessed prior to and during lithium therapy. Routine urinalysis and other tests may be used to evaluate tubular function (e.g., urine specific gravity or osmolality following a period of water deprivation, or 24-hour urine volume) and glomerular function (e.g., serum creatinine or creatinine clearance). During lithium therapy, progressive or sudden changes in renal function, even within the normal range, indicate the need for reevaluation of treatment.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic, most notably haloperidol. In some instances, the syndrome was followed by irreversible brain damage. Because of possible causal relationship between these events and the concomitant administration of lithium and neuroleptic drugs, patients receiving such combined therapy or patients with organic brain syndrome or other CNS impairment should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as Neuroleptic Malignant Syndrome (NMS).

Lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to the therapeutic concentrations (see DOSAGE AND ADMINISTRATION).

Outpatients and their families should be warned that the patient must discontinue lithium therapy and contact his physician if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur.

Lithium may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

Usage in Pregnancy: Adverse effects on nidation in rats, embryo viability in mice, and metabolism in vitro of rat testis and human spermatozoa have been attributed to lithium, as have teratogenicity in submammalian species and cleft palate in mice.

In humans, lithium may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other anomalies, especially Ebstein's anomaly. If this drug is used in women of childbearing potential, or during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised by their physician of the potential hazard to the fetus.

Usage in Nursing Mothers: Lithium is excreted in human milk. Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the view of the physician, the potential benefits to the mother outweigh possible hazard to the child. Signs and symptoms of lithium toxicity such as hypertonia, hypothermia, cyanosis and ECG changes have been reported in some infants.

Usage in Children: Since the safety and effectiveness of lithium in children under 12 years of age has not been established, its use in such patients is not recommended at this time.

There has been a report of transient syndrome of acute dystonia and hyperreflexia occurring in a 15 kg child who ingested 300 mg of lithium carbonate.

PRECAUTIONS:

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside (see DOSAGE AND ADMINISTRATION).

The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in feces. Renal excretion of lithium is proportional to its plasma concentration. The elimination half-life of lithium is approximately 24 hours. Lithium decreases sodium reabsorption by the renal tubules which could lead to sodium depletion. Therefore, it is essential for the patient to maintain a normal diet, including salt, and an adequate fluid intake (2500-3500 mL) at least during the initial stabilization period. Decreased tolerance to lithium has been reported to ensue from protracted sweating or diarrhea and, if such occur, supplemental fluid and salt should be administered under careful medical supervision and lithium intake reduced or suspended until the condition is resolved.

In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Previously existing thyroid disorders do not necessarily constitute a contraindication to lithium treatment. Where hypothyroidism preexists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters and/or adjustment of lithium doses, if any. If hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

In general, the concomitant use of diuretics or angiotensin converting enzyme (ACE) inhibitors with lithium carbonate should be avoided. In those cases where concomitant use is necessary extreme caution is advised since sodium loss from these drugs may reduce the renal clearance of lithium resulting in increased serum lithium concentrations with the risk of lithium toxicity. When such combinations are used, the lithium dosage may need to be decreased, and more frequent monitoring of lithium serum concentrations is recommended. See WARNINGS for additional caution information.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

The following drugs can lower serum lithium concentrations by increasing urinary lithium excretion: acetazolamide, urea, xanthine preparations and alkalinizing agents such as sodium bicarbonate.

Concomitant extended use of iodide preparations, especially potassium iodide, with lithium may produce hypothyroidism. Indomethacin and piroxicam have been reported to significantly increase steady state serum lithium concentrations. In some cases lithium toxicity has resulted from such interactions. There is also some evidence that other nonsteroidal, anti-inflammatory agents may have a similar effect. When such combinations are used, increased serum lithium concentrations monitoring is recommended.

LITHOBID[®] (Lithium Carbonate, USP) Slow-Release Tablets, 300 mg

Concurrent use of calcium channel blocking agents with lithium may increase the risk of neurotoxicity in the form of ataxia, tremors, nausea, vomiting, diarrhea and/or trinitus. Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. Patients receiving such combined therapy should be monitored closely.

Concurrent use of fluoxetine with lithium has resulted in both increased and decreased serum lithium concentrations. Patients receiving such combined therapy should be monitored closely.

Lithium may impair mental and/or physical abilities. Patients should be cautioned about activities requiring alertness (e.g., operating vehicles or machinery).

Usage in Pregnancy: Pregnancy Category D (see WARNINGS).

Usage in Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from lithium, 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 (see WARNINGS).

Usage in Children: Safety and effectiveness in children below the age of 12 have not been established (see WARNINGS).

Usage in the Elderly: Elderly patients often require lower lithium dosages to achieve therapeutic serum concentrations. They may also exhibit adverse reactions at serum concentrations ordinarily tolerated by younger patients. Additionally, patients with renal impairment may also require lower lithium doses (see WARNINGS).

ADVERSE REACTIONS:

The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations and to individual patient sensitivity to lithium. They generally occur more frequently and with greater severity at higher concentrations.

Adverse reactions may be encountered at serum lithium concentrations below 1.5 mEq/L. Mild to moderate adverse reactions may occur at concentrations from 1.5-2.5 mEq/L, and moderate to severe reactions may be seen at concentrations from 2.0 mEq/L and above.

Fine hand tremor, polyuria and mild thirst may occur during initial therapy for the acute manic phase, and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration.

These side effects usually subside with continued treatment or with a temporary reduction or cessation of dosage. If persistent, a cessation of lithium therapy may be required. Diarrhea, vomiting, drowsiness, muscular weakness and lack of coordination may be early signs of lithium intoxication, and can occur at lithium concentrations below 2.0 mEq/L. At higher concentrations giddiness, ataxia, blurred vision, trinitus and a large output of dilute urine may be seen. Serum lithium concentrations above 3.0 mEq/L may produce a complex clinical picture involving multiple organs and organ systems. Serum lithium concentrations should not be permitted to exceed 2.0 mEq/L during the acute treatment phase.

The following reactions have been reported and appear to be related to serum lithium concentrations, including concentrations within the therapeutic range:

Central Nervous System: tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), hyperreflexia, ataxia, choreoathetotic movements, hyperactive deep tendon reflex, extrapyramidal symptoms including acute dystonia, cogwheel rigidity, blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, downbeat nystagmus, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, tongue movements, tics, trinitus, hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes. Cases of Pseudotumor Cerebri (increased intracranial pressure and papilloedema) have been reported with lithium use. If undetected, this condition may result in enlargement of the blind spot, constriction of visual fields and eventual blindness due to optic atrophy. Lithium should be discontinued, if clinically possible, if this syndrome occurs.

Cardiovascular: cardiac arrhythmia, hypotension, peripheral circulatory collapse, bradycardia, sinus node dysfunction with severe bradycardia (which may result in syncope); **Gastrointestinal:** anorexia, nausea, vomiting, diarrhea, gastritis, salivary gland swelling, abdominal pain, excessive salivation, flatulence, indigestion; **Genitourinary:** glycosuria, decreased creatinine clearance, albuminuria, oliguria, and symptoms of nephrogenic diabetes insipidus including polyuria, thirst and polydipsia; **Dermatologic:** drying and thinning of hair, alopecia, anesthesia of skin, acne, chronic folliculitis, xerosis cutis, psoriasis or its exacerbation, generalized pruritus with or without rash, cutaneous ulcers, angiodema; **Autonomic Nervous System:** blurred vision, dry mouth, impotence/sexual dysfunction; **Thyroid Abnormalities:** euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T₃ and T₄. ¹³¹Iodine uptake may be elevated (see PRECAUTIONS).

Paradoxically, rare cases of hyperthyroidism have been reported. **EEG Changes:** diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm. **EKG Changes:** reversible flattening, isoelectricity or inversion of T-waves. **Miscellaneous:** Fatigue, lethargy, transient scotomata, exophthalmos, dehydration, weight loss, leukocytosis, headache, transient hyperglycemia, hypercalcemia, hyperparathyroidism, albuminuria, excessive weight gain, edematous swelling of ankles or wrists, metallic taste, dysgeusia/taste distortion, salty taste, thirst, swollen lips, tightness in chest, swollen and/or painful joints, fever, polyarthralgia, and dental caries.

Some reports of nephrogenic diabetes insipidus, hyperparathyroidism and hypothyroidism which persist after lithium discontinuation have been received.

A few reports have been received of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of starting lithium treatment. The mechanism through which these symptoms (resembling Raynaud's Syndrome) developed is not known. Recovery followed discontinuance.

OVERDOSAGE:

The toxic concentrations for lithium (≥ 1.5 mEq/L) are close to the therapeutic concentrations (0.6-1.2 mEq/L). It is therefore important that patients and their families be cautioned to watch for early toxic symptoms and to discontinue the drug and inform the physician should they occur. (Toxic symptoms are listed in detail under ADVERSE REACTIONS).

Treatment: No specific antidote for lithium poisoning is known. Treatment is supportive. Early symptoms of lithium toxicity can usually be treated by reduction or cessation of dosage of the drug and resumption of the treatment at a lower dose after 24 to 48 hours. In severe cases of lithium poisoning, the first and foremost goal of treatment consists of elimination of this ion from the patient.

Treatment is essentially the same as that used in barbiturate poisoning: 1) gastric lavage, 2) correction of fluid and electrolyte imbalance and 3) regulation of kidney functioning. Urea, mannitol, and aminophylline all produce significant increases in lithium excretion. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient. However, patient recovery may be slow.

Infection prophylaxis, regular chest X-rays, and preservation of adequate respiration are essential.

SOLVAY PHARMACEUTICALS

Marietta, GA 30062

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PAXIL® (brand of paroxetine hydrochloride)

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or PDR. The following is a brief summary.

INDICATIONS AND USAGE: *Paxil* is indicated for the treatment of depression, obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in DSM-IV, and panic disorder, with or without agoraphobia, as defined in DSM-IV.

CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. (See WARNINGS and PRECAUTIONS.)

WARNINGS: Interactions with MAOIs may occur. Given the fatal interactions reported with concomitant or immediately consecutive administration of MAOIs and other SSRIs, do not use *Paxil* in combination with a MAOI or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping *Paxil* before starting a MAOI.

PRECAUTIONS: As with all antidepressants, use *Paxil* cautiously in patients with a history of mania. Use *Paxil* cautiously in patients with a history of seizures. Discontinue it in any patient who develops seizures.

The possibility of suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Write *Paxil* prescriptions for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Reversible hyponatremia has been reported, mainly in elderly patients, patients taking diuretics or those who were otherwise volume depleted. Abnormal bleeding (mostly ecchymosis and purpura), including a case of impaired platelet aggregation, has been reported; the relationship to paroxetine is unclear.

Clinical experience with *Paxil* in patients with concomitant systemic illness is limited. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Observe the usual cautions in cardiac patients. In patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment, a lower starting dose (10 mg) should be used.

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that *Paxil* therapy does not affect their ability to engage in such activities. Tell patients 1) to continue therapy as directed; 2) to inform physicians about other medications they are taking or plan to take; 3) to avoid alcohol while taking *Paxil*; 4) to notify their physicians if they become pregnant or intend to become pregnant during therapy, or if they're nursing.

Weakness, hyperreflexia, and incoordination following use of an SSRI and sumatriptan have been rarely reported.

Concomitant use of *Paxil* with tryptophan is not recommended. Use cautiously with warfarin. When administering *Paxil* with cimetidine, dosage adjustment of *Paxil* after the 20 mg starting dose should be guided by clinical effect. When co-administering *Paxil* with phenobarbital or phenytoin, no initial *Paxil* dosage adjustment is needed, base subsequent changes on clinical effect. Concomitant use of *Paxil* with drugs metabolized by cytochrome P₄₅₀2D₆ (antidepressants such as nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine; phenothiazines such as thioridazine; Type 1C antiarrhythmics such as propafenone, flecainide and encainide) or with drugs that inhibit this enzyme (e.g., quinidine) may require lower doses than usually prescribed for either *Paxil* or the other drug; approach concomitant use cautiously. An *in vivo* interaction study revealed that paroxetine had no effect on terfenadine pharmacokinetics. Additional *in vitro* studies showed that the inhibitory effects of paroxetine on other IIIA₂ substrates (astemizole, cisapride, triazolam and cyclosporin) was at least 100 times less potent than ketoconazole, a potent IIIA₂ inhibitor. Assuming that the relationship between paroxetine's *in vitro* Ki and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other IIIA₂ substrates, paroxetine's inhibition of IIIA₂ activity should have little clinical significance. Use caution when co-administering *Paxil* with tricyclic antidepressants (TCAs). TCA plasma concentrations may need monitoring and the TCA dose may need to be reduced. Administration of *Paxil* with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug. Concomitant use of *Paxil* and alcohol in depressed patients is not advised. Undertake concomitant use of *Paxil* and lithium or digoxin cautiously. If adverse effects are seen when co-administering *Paxil* with procyclidine, reduce the procyclidine dose. Elevated theophylline levels have been reported with *Paxil* co-administration; monitoring theophylline levels is recommended.

In 2-year studies, a significantly greater number of male rats in the 20 mg/kg/day group developed reticulum cell sarcomas vs. animals given doses of 1 or 5 mg/kg/day. There was also a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The clinical significance of these findings is unknown. There is no evidence of mutagenicity with *Paxil*.

Rats receiving paroxetine at 15 mg/kg/day (2.4 times the MRHD on a mg/m² basis) showed a reduced pregnancy rate.

Pregnancy Category C. Reproduction studies performed in rats and rabbits at doses up to 6 mg/kg/day, 8.1 (rat) and 1.9 (rabbit) times the MRHD on a mg/m² basis, have revealed no evidence of teratogenic effects or of selective toxicity to the fetus. However, rat pup deaths increased during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. *Paxil* should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. The effect of *Paxil* on labor and delivery in humans is unknown. Paroxetine is secreted in human milk; exercise caution when administering *Paxil* to a nursing woman.

Safety and effectiveness in the pediatric population have not been established. In worldwide premarketing *Paxil* clinical trials, 17% of *Paxil*-treated patients were ≥65 years of age. Pharmacokinetic studies revealed a decreased clearance in the elderly; however, there were no overall differences in the adverse event profile between older and younger patients.

ADVERSE REACTIONS: Incidence in Controlled Trials—Commonly Observed Adverse Events in Controlled Clinical Trials: The most commonly observed adverse events associated with the use of *Paxil* in the treatment of depression (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo) were: asthenia (15% vs. 6%), sweating (11% vs. 2%), nausea (26% vs. 9%), decreased appetite (6% vs. 2%), somnolence (23% vs. 9%), dizziness (13% vs. 6%), insomnia (13% vs. 6%), tremor (6% vs. 2%), nervousness (5% vs. 3%), ejaculatory disturbance (13% vs. 0%) and other male genital disorders (10% vs. 0%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of obsessive compulsive disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo) were: nausea (23% vs. 10%), dry mouth (18% vs. 9%), decreased appetite (9% vs. 3%), constipation (16% vs. 6%), dizziness (12% vs. 6%), somnolence (24% vs. 7%), tremor (11% vs. 1%), sweating (9% vs. 3%), impotence (8% vs. 1%) and abnormal ejaculation (23% vs. 1%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of panic disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo) were: asthenia (14% vs. 5%), sweating (14% vs. 6%), decreased appetite (7% vs. 3%), libido decreased (9% vs. 1%), tremor (9% vs. 1%), abnormal ejaculation (21% vs. 1%), female genital disorders (9% vs. 1%) and impotence (5% vs. 0%).

Twenty percent (1,199/6,145) of *Paxil* patients in worldwide clinical trials in depression and 11.8% (64/542) and 9.4% (44/469) of *Paxil* patients in worldwide trials in OCD and panic disorder, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related include the following: depression—somnolence, agitation, tremor, nausea, diarrhea, dry mouth, vomiting, asthenia, abnormal ejaculation, sweating;

OCD—insomnia, dizziness, constipation, nausea, asthenia, abnormal ejaculation, impotence; panic disorder—somnolence, insomnia, nausea.

The following adverse events occurred in 6-week placebo-controlled trials of similar design at a frequency of 1% or more, in patients dosed (20 to 50 mg/day) for the treatment of depression: headache, asthenia, palpitation; vasodilation; sweating, rash; nausea, dry mouth, constipation, diarrhea, decreased appetite, flatulence, oropharynx disorder, dyspepsia; myopathy, myalgia, myasthenia; somnolence, dizziness, insomnia, tremor, nervousness, anxiety, paresthesia, libido decreased, drugged feeling, confusion; yawn; blurred vision, taste perversion; ejaculatory disturbance, other male genital disorders, urinary frequency, urination disorder, female genital disorders.

The following adverse events occurred at a frequency of 2% or more among OCD patients on *Paxil* who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 to 60 mg/day or among patients with panic disorder on *Paxil* who participated in placebo-controlled trials of 10 to 12 weeks duration in which patients were dosed in a range of 10 to 80 mg/day: asthenia, abdominal pain**, chest pain**, back pain**, chills; vasodilation**, palpitation**, sweating, rash**, nausea, dry mouth, constipation, diarrhea, decreased appetite, increased appetite; insomnia, somnolence, dizziness, tremor, nervousness**, libido decreased, agitation**, anxiety**; abnormal dreams**, concentration impaired**, depersonalization**, myoclonus, amnesia**, rhinitis**, abnormal vision**, taste perversion**; abnormal ejaculation, female genital disorder, impotence, urinary frequency, urination impairment**, urinary tract infection. **denotes panic disorder patients only. **denotes OCD patients only.

Studies show a clear dose dependency for some of the more common adverse events associated with *Paxil* use. There was evidence of adaptation to some adverse events with continued *Paxil* therapy (e.g., nausea and dizziness). Significant weight loss may be an undesirable result of *Paxil* treatment for some patients but, on average, patients in controlled trials had minimal (about 1 lb) loss. In placebo-controlled clinical trials, *Paxil*-treated patients exhibited abnormal values on liver function tests no more frequently than placebo-treated patients.

Other Events Observed During the Premarketing Evaluation of *Paxil*: During premarketing assessment in depression multiple doses of *Paxil* were administered to 6,145 patients in phase 2 and 3 studies. During premarketing clinical trials in OCD and panic disorder, 542 and 469 patients, respectively, received multiple doses of *Paxil*. The following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients; "rare" = less than 1/1000 patients. Events are classified within body system categories and enumerated in order of decreasing frequency using the above definitions. It is important to emphasize that although the events occurred during *Paxil* treatment, they were not necessarily caused by it.

Body as a Whole: frequent: chills, malaise; infrequent: allergic reaction, carcinoma, face edema, moniliasis, neck pain; rare: abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, shock, ulcer. **Cardiovascular System:** frequent: hypertension, syncope, tachycardia; infrequent: bradycardia, conduction abnormalities, electrocardiogram abnormal, hematoma, hypotension, migraine, peripheral vascular disorder; rare: angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, plebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System: frequent: bruxism, colitis, dysphagia, eructation, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage, ulcerative stomatitis; rare: aphthous stomatitis, bloody diarrhea, bulimia, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gastritis, gum hemorrhage, hematemeses, hepatitis, ileus, intestinal obstruction, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries, tooth malformation. **Endocrine System:** rare: diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis. **Hemic and Lymphatic Systems:** infrequent: anemia, leukopenia, lymphadenopathy, purpura; rare: abnormal erythrocytes, basophilia, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocytopenia.

Metabolic and Nutritional: frequent: edema, weight gain, weight loss; infrequent: hyperglycemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare: alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesterolemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased. **Musculoskeletal System:** frequent: arthralgia; infrequent: arthritis; rare: arthrosis, bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany. **Nervous System:** frequent: amnesia, CNS stimulation, concentration impaired, depression, emotional lability, vertigo; infrequent: abnormal thinking, akinesia, alcohol abuse, ataxia, convulsion, depersonalization, dystonia, hallucinations, hostility, hyperkinesia, hypertension, hyposthesia, incoordination, lack of emotion, manic reaction, neurosis, paralysis, paranoid reaction; rare: abnormal electroencephalogram, abnormal gait, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hypokinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus, withdrawal syndrome. **Respiratory System:** frequent: cough increased, rhinitis; infrequent: asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis, voice alteration; rare: emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased. **Skin and Appendages:** frequent: pruritus; infrequent: acne, alopecia, dry skin, ecchymosis, eczema, urticaria; rare: angioedema, contact dermatitis, erythema nodosum, erythema multiforme, fungal dermatitis, herpes simplex, herpes zoster, hirsutism, maculopapular rash, photosensitivity, seborrhea, skin discoloration, skin hypertrophy, skin melanoma, skin ulcer, vesiculobullous rash.

Special Senses: frequent: tinnitus; infrequent: abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, taste loss, visual field defect; rare: amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, keratoconjunctivitis, night blindness, otitis externa, ptosis, photophobia, ptosis, retinal hemorrhage. **Urogenital System:** infrequent: abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, hematuria, menorrhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis; rare: breast atrophy, breast carcinoma, breast enlargement, breast neoplasm, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney function abnormal, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, prostatic carcinoma, pyuria, urethritis, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

Postmarketing Reports
Voluntary reports of adverse events that have been received since market introduction and not listed above that may have no causal relationship with *Paxil* include—acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, thrombocytopenia, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertension, oculogyric crisis (which has been associated with concomitant use of pimozide), tremor and trismus; and serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired *Paxil* metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor). There have been spontaneous reports that abrupt discontinuation may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating; these events are generally self-limiting. There has been a report of an elevated phenytoin level after 4 weeks of *Paxil* and phenytoin co-administration, and a report of severe hypotension when *Paxil* was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: *Paxil* is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of *Paxil* misuse or abuse (e.g., development of tolerance, increments of dose, drug-seeking behavior).
BRS-PXL12



The symptoms may overlap... but the solution is the same

CONTROLS
OCD

RELIEVES
PANIC DISORDER

LIFTS
DEPRESSION

Most common adverse events (incidence of 5% or greater and incidence for Paxil at least twice that for placebo) in depression or OCD or panic disorder studies include nausea, somnolence, abnormal ejaculation, dry mouth, constipation, asthenia, sweating, dizziness, insomnia, tremor, female genital disorders, libido decreased, decreased appetite, impotence and nervousness. Concomitant use of Paxil in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated.

Please see brief summary of prescribing information at the end of this advertisement.

ONCE-DAILY
PAXIL
PAROXETINE HCl

Lifts depression. Lowers associated anxiety symptoms.

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PHOTO ESSAY

Maze-solving behavior as a tool for the investigation of cognitive disturbance in schizophrenic patients may permit insight into specific impairments in disease-related cognitive processing by testing domains that are preferentially disturbed in schizophrenia.

In this issue, Gallhofer et al, present the results of a maze task study comparing medication-free schizophrenic patients and matched healthy controls, forming the basis for an investigation of the influence of psychopharmacologic treatment strategies.

This issue of CNS Spectrums is dedicated to the memory of Matthew Pilkington Nemeroff (7/17/81-8/9/97).

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In the medical management of ADHD...

**SOAR CONFIDENTLY
INTO SUMMER
AND THE NEW SCHOOL YEAR.**

TRY ADDERALL[®]—

IT MAY MAKE A DIFFERENCE

Summertime may be an ideal time to try a different ADHD treatment plan:

- There are no daily school routines to interrupt while determining the proper medication and dosing regimen for optimum results
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ADDERALL—the only ADHD product available that contains both dextro (*d*) and levo (*l*) amphetamine—may make a difference for some patients

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- ADDERALL usage data indicate that most patients were therapeutically maintained on doses as low as 5 mg a day and doses no higher than 20 mg a day^{1*}
- ADDERALL 10 mg and 20 mg double-scored tablets provide optimal dosing flexibility for physicians and patients
- ADDERALL offers a profile of safety, efficacy, and tolerability you can feel comfortable with in children 3 years of age and older²

As with most psychostimulants indicated for ADHD, the possibility of growth suppression and the potential for precipitating motor tics and Tourette's Syndrome exists with ADDERALL treatment, and in rare cases exacerbations of psychosis have been reported.²

Since amphetamines have a high potential for abuse, ADDERALL should only be prescribed as part of an overall multimodal treatment program for ADHD with close physician supervision.



10-mg blue double-scored tablet



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10 mg & 20 mg TABLETS
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Amphetamine Sulfate
Dextroamphetamine Saccharate Amphetamine Aspartate

*Thirty-four patients receiving greater than 40 mg per day were excluded from this analysis



Richwood Pharmaceutical Company Inc.

...working to become your ADHD support company

Please see references and brief summary of prescribing information on adjacent page.

REFERENCES: 1. Data on file, Richwood Pharmaceutical Company Inc. Analysis of open-label data collected from March 1995 through February 1996.
2. ADDERALL package insert, Richwood Pharmaceutical Company Inc.

ADDERALL 

10 mg & 20 mg TABLETS
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Amphetamine Sulfate
Dextroamphetamine Saccharate Amphetamine Aspartate

ADDERALL® TABLETS  BRIEF SUMMARY

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. 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.

INDICATIONS: Attention Deficit Disorder with Hyperactivity: ADDERALL is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted. **In Narcolepsy: 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:** Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment. **Usage in Nursing Mothers:** Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing. **PRECAUTIONS: General:** Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. **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, fruit juices, etc.) lower absorption of amphetamines. **Urinary acidifying 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. **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 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 neurological toxic 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 reuptake, 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 and norepinephrine reuptake, 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. **Methamphetamine therapy -** Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methamphetamine 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:** Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of amphetamine, have not been performed. **Pregnancy - Teratogenic Effects:** Pregnancy Category C. Amphetamine has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no

adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal 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. **Pediatric Use:** 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 with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE. 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. Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics. When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated. **ADVERSE REACTIONS: Cardiovascular:** Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. **Central Nervous System:** Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome. **Gastrointestinal:** Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. **Allergic:** Urticaria. **Endocrine:** Impotence, changes in libido. **DRUG ABUSE AND DEPENDENCE:** Dextroamphetamine sulfate 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 include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines. **OVERDOSAGE:** Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal. In rats, the oral LD50 of dextroamphetamine sulfate is 96.8 mg/kg. **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 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 (Regitine®, CIBA) 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. **DOSAGE AND ADMINISTRATION:** Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia. **Attention Deficit Disorder with Hyperactivity:** Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained. In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. **Narcolepsy:** Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response. Narcolepsy seldom occurs in children under 12 years of age; however, when it does dextroamphetamine sulfate, may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. **CAUTION:** Federal law prohibits dispensing without prescription.



Richwood Pharmaceutical Company Inc.

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Revised: February 1997