NDA 16-012/S-038; S-044; S-046

Merck Research Laboratories
Attention: Dennis M. Erb, Ph.D.
Sumheytown Pike, P.O. Box 4
BL A-20
West Point, PA 19486 Dear Dr. Erb:

MAR 2 7 2000

Please refer to your supplemental new drug applications dated December 6, 1985, October 13, 1994, and February 1,1996, received December 9, 1985, October 18, 1994, and February 2, 1996, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIVACTIL (protryptyline HCI), 5 mg and 10 mg Tablets.

We also refer to an Agency approval letter dated April 13, 1987, for FPL (7398519) submitted under supplemental application 5-040.

Supplemental application S-038 provides revised final printed labeling that incorporates the following changes:

1. the deletion of the second sentence in WARNINGS as requested by the Agency in a letter dated August 6, 1985. This sentence is a repeat of information in PRECAUTIONS/ *In formation for Patients* and it reads:

   > "It may impair mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery. or driving a motor vehicle."

2. the inclusion of a statement regarding cimetidine/tricyclic antidepressant interactions as requested by the Agency in a letter dated August 6,1985.

3. the inclusion of an *In formation for Patients* subsection under PRECAUTIONS which describes the possible mental and/or physical impairment. This sentence is consistent with the text found in TRIAVIL labeling and the Agency letter dated August 6, 1985.

We note that supplemental application S-040, approved on April 23, 1987, supercedes supplemental application S-038. Therefore, we will not take action on supplemental application S-038 but it will be retained in our files.

Supplemental application S-044 provides the creation of the *Drug Interactions* subsection under the PRECAUTIONS section of labeling and the incorporation of language relating to drugs metabolized by P 450 2D6 as described in an Agency letter dated June 15, 1994 to Dr. John Beary of PhRMA.

Supplement application S-046 provides revision of the OVERDOSAGE section of labeling in response to an Agency letter dated October 3, 1995, in order to describe current clinical toxicology recommendations on how to best manage overdoses with tricyclic antidepressants. The revised text was taken, in most part, from a core labeling document submitted by Dr. John Siegfried of PhRMA on January 26, 1996.

We have completed the review of these supplemental applications (S-044 and S-046) and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling (copy code 7904022) submitted on February 1,1996. Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a “Dear Health Care Practitioner’ letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Merril Mille, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

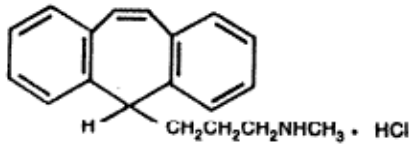
Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

TABLETS

VIVACTIL®
(PROTRIPTYLINE HCI)

DESCRIPTION

Protriptyline HCI is N-methyl-5H-dibenzo [a,d]-cycloheptene-5-propanamine hydrochloride, Its empirical formula is C19H21N• HCI and its structural formula is:



Protriptyline HCI, a dibenzocyctoheptene derivative, has a molecular weight of 299.84. It is a white to yellowish powder that is freely soluble in water and soluble in dilute HCI.

VIVACTIL* (Protriptyline HCI) is supplied as 5 mg and 10 mg film coated tablets. Inactive ingredients are calcium phosphate, cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, starch, talc, and titanium dioxide. Tablets VIVACTIL S mg and 10 mg also contain FD&C Yellow 6. Tablets VIVACTIL 10 mg also contain D&C Yellow 10.

ACTIONS

VIVACTIL is an antidepressant agent. The mechanism of its antidepressant action in man is not known. It is not a monoamine oxidas.e inhibitor, and it does not act primarily by stimulation of the central nervous system.

VIVACTIL has been found in some studies to have a more rapid onset of action than imipramine or amitriptyline. The initial clinical effect may occur within one week. Sedative and tranquilizing properties are lacking. The rate of excretion is slow.

INDICATIONS

VIVACTIL is indicated for the treatment of symptoms of mental depression in patients who are under close medical supervision. Its activating properties make it particularly suitable for withdrawn and anergic patients.

CONTRAINDICATIONS

VIVACTIL is contraindicated in patients who have shown prior hypersensitivity to it.

It should not be given concomitantly with a monoamine oxidase inhibiting compound. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and monoamine oxidase inhibiting drugs simultaneously. When it is desired to substitute VIVACTIL for a monoamine oxidase inhibitor, a minimum of 14 days should be allowed to elapse after the latter is discontinued. VIVACTIL should then be initialed cautiously with gradual increase in dosage until optimum response is achieved.

This drug should not be used during the acute recovery phase following myocardial infarction.

WARNINGS

VIVACTIL may block the antihypertensive effect of guanethidine or similarly acting compounds.

VIVACTIL should be used with caution in patients with a history of seizures, and, because of its autonomic activity, in patients with a tendency to urinary retention, or increased intraocular tension.

Tachycardia and postural hypotension may occur more frequently with VIVACTIL than with other antidepressant drugs. VIVACTIL should be used with caution in elderly patients and patients with cardiovascular disorders; such patients should be observed closely because of the tendency of the drug to produce tachycardia, hypotension, arrhythmias, and prolongation of the conduction time. Myocardial infarction and stroke have occurred with drugs of this class.

On rare occasions, hyperthyroid patients or those receiving thyroid medication may develop arrhythmias when this drug is given.

In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

Usage in Children

This drug is not recommended for use in children because safety and effectiveness in the pediatric age group have not been established.

Usage in Pregnancy

Safe use in pregnancy and lactation has not beenestablished; therefore, use in pregnant women, nursing mothers or women who may become pregnant requires that possible benefits be weighed against possible hazards to mother and child.

In mice, rats, and rabbits, doses about ten times greater than the recommended human doses had no apparent adverse effects on reproduction.

PRECAUTIONS

General

When protriptyline HCl is used to treat the depressive component of schizophrenia, psychotic symptoms may be aggravated. Likewise, in manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant drug. Paranoid delusions, with or without associated hostility, may be exaggerated. In any of these circumstances, it may be advisable to reduce the dose of VIVACTIL or to use a major tranquilizing drug concurrently.

Symptoms, such as anxiety or agitation, may be aggravated in overactive or agitated patients.

The possibility of suicide in depressed patients remains during treatment and until significant remission occurs. This type of patient should not have access to large quantities of the drug.

Concurrent administration of VIVACTIL and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to patients for whom it is essential.

Discontinue the drug several days before elective surgery, if possible.

Both elevation and lowering of blood sugar levels have been reported.

Information for Pa ients

While on therapy with VIVACTIL, patients should be advised as to the possible impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Drug Interactions

When VIVACTIL is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine, Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen. Discontinuation of cimetidine in well-controlled patients receiving tricyclic antidepressants and cimetidine may decrease the plasma levels and efficacy of the antidepressants.

It may enhance the response to alcohol and the effects of barbiturates and other ONS depressants.

Drugs Metabolized by Cytochrome P450 2D6: The biochemical activity of the drug-metabolizing isozyme, cytochrome P450 2D6 (debrisoquine hydroxylase), is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are sub-strates for P450 2D6 (many other antidepressants. phenothiazines, and the Type 1C antiarrhythmics,

propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs, and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic anfidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tnicyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tri-cyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

ADVERSE REACTIONS

Within each category the following adverse reactions are listed in order of decreasing severity. Included in the listing are a few adverse reactions which have not been reported with this specific drug. However, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when protriptyline is administered. VIVACTIL is more likely to aggravate agitation and anxiety and produce cardiovascular reactions such as tachycardia and hypotension.

Cardiovascular: Myocardial infarction; stroke; heart block; arrhythmias; hypotension, particularly orthostatic hypolonsion; hypertension; tachycardia; palpilation.

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; hypomania; exacerbation of psychosis; insomnia, panic, and nightmares.

Neurological: Seizures; incoordination; ataxia; tremors; peripheral neuropathy; numbness, tingling, and paresthesias of extremities; extrapyramidal symptoms; drowsiness; dizziness; weakness and fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.

Anticholinergic:Paralytic ileus; hyperpyrexia; urinary retention, delayed micturition, dilatation of the urinary tract; constipation; blurred vision, disturbance of accommodation, increased intraocular pressure, mydriasis; dry mouth and rarely associated sublingual adenitis.

Allergic: Drug fever; petechiae; skin rash, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general, or of face and tongue).

Hematologic: Agranulocytosis; bone marrow depression; leukopenia; thrombocytopenia; purpura; eosinophilia.

Gasfrointestinal: Nausea and vomiting; anorexia; epigastric distress; diarrhea; peculiar taste; stomatitis; abdominal cramps; black tongue.

Endocrine: Impotence, increased or decreased libido; gynecomastia in the male; breast enlargement and galactorrhea in the female; testicular swelling; elevation or depression of blood sugar levels.

Other: Jaundice (simulating obstructive); altered liver function; parotid swelling; alopecia; flushing; weight gain or loss; urinary frequency, nocturia; perspiration.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Usual Adult Dosage — Fifteen to 40 mg a day divided into 3 or 4 doses. If necessary, dosage may be increased to 60 mg a day. Dosages above this amount are not recommended. Increases should be made in the morning dose.

Adolescent and *Elderly Patients* — In general, lower dosages are recommended for these patients. Five mg 3 times a day may be given initially, and increased gradually if necessary. In elderly patients, the cardiovascular system must be monitored closely if the daily dose exceeds 20 mg.

When satisfactory improvement has been reached, dosage should be reduced to the smallest amount that will maintain relief of symptoms.

Minor adverse reactions require reduction in dosage. Major adverse reactions or evidence of hypersensitivity require prompt discontinuation of the drug.

Usage in Children — This drug is not recommended for use in children because safety and effectiveness in the pediatric age group have not been established.

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose, therefore, hospital monitoring is required as soon as possible.

MANIFESTATIONS

Critical manifestations of overdosage include: cardiac dysrhythmias, severe hypotension, convulsions, and ONS depression, including coma. Changes in the electrocardiogram, particularly in ORS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under ADVERSE REACTIONS.

MANAGEMENT

General

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiralory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period. extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose. These patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination

All patients suspected of a tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of >0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation las needed), should be instituted for patients with dysrhythmias and/or ORS widening. A pH $\geq$7.60 or a pCO2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/ hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamidel.

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoinl. Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.

PSYCHIATRIC FOLLOW-UP

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

PEDIATRIC MANAGEMENT

The principles of management of child and adult overdosages are similar, It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

HOW SUPPLIED

No. 3313— Tablets VIVACTIL, 5 mg, are orange, oval, film coated tablets, coded MSD 26. They are supplied as follows:

NDC 0006-0026-68 bottles of 100.

(6505-00-369-7297,5mg 100).

No. 3314— Tablets VIVACTIL, 10 mg, are yellow, oval, film coated tablets, coded MSD 47. They are supplied as follows:

NDC 0006-0047-68 bottles of 100

(6505-00-462-7353, 10 mg l00s)

NDC 0006-0047-28 unit dose packages of 100.

Storage

Store Tablets VIVACTIL in a tightly closed container. Avoid storage at temperatures above 40°C (104°F).

METABOLISM

Metabolic studies indicate that protriptyline is well absorbed from the gastrointestinal tract and is rapidly sequestered in tissues. Relatively low plasma levels are found after administration, and onlya small amount of unchanged drug is excreted in the urine of dogs and rabbits. Preliminary studies indicate that demethylation of the secondary amine moiety occurs to a significant extent, and that metabolic transformation probably takes place in the liver, It penetrates the brain rapidly in mice and rats, and moreover that which is present in the brain is almost all unchanged drug.

Studies on the disposition of radioactive protriptyline in human test subjects showed significant plasma levels within 2 hours, peaking at 8 to 12 hours, then declining gradually.

Urinary excretion studies in the same subjects showed significant amounts of radioactivity in 2 hours. The rate of excretion was slow. Cumulative urinary excretion during 16 days accounted for approximately 50% of the drug. The fecal route of excretion did not seem to be important.

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