CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040218

Trade Name : AMITRIPTYLINE HCL TABLETS USP

Generic Name: Amitriptyline Hcl Tablets 10mg, 25mg, 50mg, 75mg, 100mg and 150mg

Sponsor : Vintage Pharmaceuticals, Inc

Approval Date: September 11, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040218

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EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040218

APPROVAL LETTER

ANDA 40-218

SEP 11 1997

Vintage Pharmaceuticals, Inc.
Attention: Rebecca Thurman
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Madam:

This is in reference to your abbreviated new drug application dated November 1, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Amitriptyline Hydrochloride Tablets USP, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg.

Reference is also made to your amendments dated July 23, and August 29, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Amitriptyline Hydrochloride Tablets USP, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg and 150 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Elavil® Tablets, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg and 150 mg, respectively, of Zeneca Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253

(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Spurlin
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

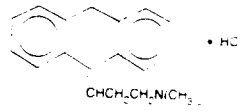
APPLICATION NUMBER 040218

FINAL PRINTED LABELING

AMITRIPTYLINE HYDROCHLORIDE TABLETS, USP

DESCRIPTION

Amitriptyline HCl is 10,11-Dihydro-N, N-dimethyl-5H-dibenzo[a,d]cycloheptene-Δ[illegible]γ-propylamine hydrochloride; its molecular formula is $C_{20}H_{23}N \cdot HCl$, and its structural formula is



$\cdot HCl$

$CHCH_2CH_2N(CH_3)_2$

Amitriptyline HCl, a dibenzocycloheptadiene derivative, has a molecular weight of 313.87. It is a white, or practically white, odorless, crystalline compound which is freely soluble in water and alcohol.

Amitriptyline HCl is supplied as 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, or 150 mg tablets. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, hydroxypropyl methylcellulose, titanium dioxide, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate and sodium starch glycolate. The 10 mg tablets also contain D&C yellow #10 lake and FD&C Blue #1 lake. The 25 mg tablets also contain D&C yellow #10 lake and FD&C Blue #2 lake. The 50 mg tablets also contain synthetic black iron oxide, synthetic yellow iron oxide and synthetic red iron oxide. The 75 mg tablets also contain FD&C yellow #6 lake. The 100 mg tablets also contain D&C red #33 lake and FD&C red #40 lake. The 150 mg tablets also contain FD&C blue #2 lake and FD&C yellow #6 lake.

CLINICAL PHARMACOLOGY

Amitriptyline hydrochloride is an antidepressant with sedative effects. Its mechanism of action in man is not known. It is not a monoamine oxidase inhibitor and it does not act primarily by stimulation of the central nervous system.

Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Pharmacologically this action may potentiate or prolong neuronal activity since reuptake of these biogenic amines is important physiologically in terminating transmitting activity. This interference with the reuptake of norepinephrine and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline.

INDICATIONS AND USAGE

For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than are other depressive states.

CONTRAINDICATIONS

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

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

This drug is not recommended for use during the acute recovery phase following myocardial infarction.

WARNINGS

Amitriptyline hydrochloride may block the antihypertensive action of guanethidine or similarly acting compounds.

It should be used with caution in patients with a history of seizures and, because of its atropine-like action, in patients with a history of urinary retention, angle-closure glaucoma or increased intraocular pressure. In patients with angle-closure glaucoma, even average doses may precipitate an attack.

Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, including amitriptyline hydrochloride, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of the conduction time. Myocardial infarction and stroke have been reported with drugs of this class.

Close supervision is required when amitriptyline hydrochloride is given to hyperthyroid patients or those receiving thyroid medication.

Amitriptyline hydrochloride may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. 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. Delirium has been reported with concurrent administration of amitriptyline and disulfiram.

Usage in Pregnancy – Teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2 to 40 mg/kg/day (up to 13 times the maximum recommended human dose*). Studies in the literature have shown amitriptyline to be teratogenic in mice and hamsters when given by various routes of administration at doses of 28 to 100 mg/kg/day (9 to 33 times the maximum recommended human dose), producing multiple malformations. Another study in the rat reported that an oral dose of 25 mg/kg/day (8 times the maximum recommended human dose) produced delays in ossification of fetal vertebral bodies without other signs of embryotoxicity. In rabbits, an oral dose of 60 mg/kg/day (20 times the maximum recommended human dose) was reported to cause incomplete ossification of cranial bones.

Amitriptyline has been shown to cross the placenta. Although a causal relationship has not been established, there have been a few reports of adverse events, including CNS effects, limb deformities, or developmental delay, in infants whose mothers had taken amitriptyline during pregnancy.

There are no adequate or well-controlled studies in pregnant women. Amitriptyline hydrochloride should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers: Amitriptyline is excreted into breast milk. In one report in which a patient received amitriptyline 100 mg/day while nursing her infant, levels of 83 to 141 ng/mL were detected in the mother's serum. Levels of 135 to 151 ng/mL were found in the breast milk, but no trace of the drug could be detected in the infant's serum.

Because of the potential for serious adverse reactions in nursing infants from amitriptyline, 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.

Usage in Children – In view of the lack of experience with the use of this drug in children, it is not recommended at the present time for patients under 12 years of age.

PRECAUTIONS

Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms. Depressed patients, particularly those with known manic-depressive illness, may experience a shift to mania or hypomania. In these circumstances the dose of amitriptyline may be reduced or a major tranquilizer such as perphenazine may be administered concurrently.

When amitriptyline 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 amitriptyline is administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.

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.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with one gram of ethchlorvynol and 75 to 150 mg of amitriptyline hydrochloride.

The possibility of suicide in depressed patients remains until significant remission occurs. Potentially suicidal patients should not have access to large quantities of this drug. Prescriptions should be written for the smallest amount feasible.

Concurrent administration of amitriptyline hydrochloride and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential.

When possible, the drug should be discontinued several days before elective surgery.

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

Amitriptyline hydrochloride should be used with caution in patients with impaired liver function.

Drugs Metabolized by P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 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 inhibitors [illegible]

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

Information for Patients

While on therapy with amitriptyline hydrochloride, 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.

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, pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when amitriptyline is administered.

Cardiovascular: Myocardial infarction; stroke; non-specific ECG changes and changes in AV conduction; heart block; arrhythmias; hypotension, particularly orthostatic hypotension; syncope; hypertension; tachycardia; palpitation.

CNS and Neuromuscular: Coma; seizures; hallucinations; delusion; confusional states; disorientation; incoordination; ataxia;

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tremors; peripheral neuropathy; numbness; tingling and paresthesias of the extremities; extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia; dysarthria; disturbed concentration; excitement; anxiety; insomnia; restlessness; nightmares; drowsiness; dizziness; weakness; fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.

Anticholinergic: Paralytic ileus; hyperpyrexia; urinary retention, dilatation of the urinary tract; constipation; blurred vision; disturbance of accommodation, increased intraocular pressure, mydriasis, dry mouth.

Allergic: Skin rash, urticaria, photosensitization; edema of face and tongue.

Hematologic: Bone marrow depression including agranulocytosis, leukopenia, thrombocytopenia; purpura, eosinophilia.

Gastrointestinal: Rarely hepatitis (including altered liver function and jaundice); nausea; epigastric distress; vomiting, anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue.

Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; impotence; elevation and lowering of blood sugar levels.

Other: Alopecia; edema; weight gain or loss; urinary frequency; increased perspiration.

Withdrawal Symptoms: After prolonged administration, abrupt cessation of treatment may produce nausea, headache, and malaise. Gradual dosage reduction has been reported to produce, within two weeks, transient symptoms including irritability, restlessness, and dream and sleep disturbance. These symptoms are not indicative of addiction. Rare instances have been reported of mania or hypomania occurring within 2 to 7 days following cessation of chronic therapy with tricyclic antidepressants.

Causal Relationship Unknown: Other reactions, reported under circumstances where a causal relationship could not be established, are listed to serve as alerting information to physicians.

Body as a whole: Lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor).

Digestive: Hepatic failure, ageusia.

OVERDOSAGE

Manifestations – High doses may cause temporary confusion, disturbed concentration, or transient visual hallucination. Overdosage may cause drowsiness; hypothermia; tachycardia and other arrhythmic abnormalities, such as bundle branch block; ECG evidence of impaired conduction; congestive heart failure; dilated pupils; disorders of ocular motility; convulsions; severe hypotension; stupor; coma; and polyradiculoneuropathy. Other symptoms may be agitation, hyperactive reflexes, muscle rigidity, vomiting, hyperpyrexia, or any of those listed under **ADVERSE REACTIONS**.

There has been a report of fatal dysrhythmia occurring as late as 56 hours after amitriptyline overdose.

All patients suspected of having taken an overdosage should be admitted to a hospital as soon as possible. Treatment is symptomatic and supportive. Empty the stomach as quickly as possible by emesis followed by gastric lavage upon arrival at the hospital. Following gastric lavage, activated charcoal may be administered. Twenty to 30 g of activated charcoal may be given every four to six hours during the first 24 to 48 hours after ingestion. An ECG should be taken and close monitoring of cardiac function instituted if there is any sign of abnormality. Maintain an open airway and adequate fluid intake; regulate body temperature.

The intravenous administration of 1 to 3 mg of physostigmine salicylate is reported to reverse the symptoms of tricyclic antidepressant poisoning. Because physostigmine is rapidly metabolized, the dosage of physostigmine should be repeated as required particularly if life threatening signs such as arrhythmias, convulsion, and deep coma recur or persist after the initial dosage of physostigmine. Because physostigmine itself may be toxic, it is not recommended for routine use.

Standard measures should be used to manage circulatory shock and metabolic acidosis. Cardia arrhythmias may be treated with neostigmine, pyridostigmine, or propranolol. Should cardiac failure occur, the use of digitalis should be considered. Close monitoring of cardiac function for not less than five days is advisable.

Anticonvulsants may be given to control convulsions. Amitriptyline increases the CNS depressant action but not the anticonvulsant action of barbiturates; therefore, an inhalation anesthetic, diazepam, or paraldehyde is recommended for control of convulsion.

Dialysis is of no value because of low plasma concentrations of the drug.

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

Deaths by deliberate or accidental overdosage have occurred with this class of drugs.

DOSAGE AND ADMINISTRATION

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

Initial Dosage for Adults – For outpatients 75 mg of amitriptyline HCl a day in divided doses usually is satisfactory. If necessary, this may be increased to a total of 150 mg per day. Increases are made preferably in the late afternoon and/or bedtime doses. A sedative effect may be apparent before the antidepressant effect is noted, but an adequate therapeutic effect may take as long as 30 days to develop.

An alternate method of initiating therapy in outpatients is to begin with 50 to 100 mg amitriptyline HCl at bedtime. This may be increased by 25 or 50 mg as necessary in the bedtime dose to a total of 150 mg per day.

Hospitalized patients may require 100 mg a day initially. This can be increased gradually to 200 mg a day if necessary. A small number of hospitalized patients may need as much as 300 mg a day.

Adolescent and Elderly Patients – In general, lower dosages are recommended for these patients. Ten mg 3 times a day with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who do not tolerate higher dosages.

Maintenance – The usual maintenance dosage of amitriptyline HCl is 50 to 100 mg per day. In some patients 40 mg per day is sufficient. For maintenance therapy the total daily dosage may be given in a single dose preferably at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. It is appropriate to continue maintenance therapy 3 months or longer to lessen the possibility of relapse.

Usage in Children

In view of the lack of experience with the use of this drug in children, it is not recommended at the present time for patients under 12 years of age.

Plasma Levels

Because of the wide variation in the absorption and distribution of tricyclic antidepressants in body fluids, it is difficult to directly correlate plasma levels and therapeutic effect. However, determination of plasma levels may be useful in identifying patients who appear to have toxic effects and may have excessively high levels, or those in whom lack of absorption or noncompliance is suspected. Adjustment in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.**

HOW SUPPLIED

10 mg tablets are blue, round, unscored, film coated tablets, coded "2101" and "V". They are supplied in bottles of 100, 500 and 1000.

25 mg tablets are yellow, round, unscored, film coated tablets, coded "2102" and "V". They are supplied in bottles of 100, 500 and 1000.

50 mg tablets are beige, round, unscored, film coated tablets, coded "2103" and "V". They are supplied in bottles of 100, 500 and 1000.

75 mg tablets are orange, round, unscored, film coated tablets, coded "2104" and "V". They are supplied in bottles of 100, 500 and 1000.

100 mg tablets are mauve, round, unscored, film coated tablets, coded "2105" and "V". They are supplied in bottles of 100, 500 and 1000.

150 mg tablets are blue, capsule shaped, unscored, film coated tablets, coded "2106" on one side and "V" on the other side. They are supplied in bottles of 100, 500 and 1000.

Storage: Store in a well-closed container. Store at room temperature 15—30°C (59°—86°F). In addition, amitriptyline tablets must be protected from light and stored in a well-closed, light resistant container.

Caution: Federal law prohibits dispensing without prescription.

METABOLISM

Studies in man following oral administration of ^{14}C-labeled drug indicated that amitriptyline is rapidly absorbed and metabolized. Radioactivity of the plasma was practically negligible, although significant amounts of radioactivity appeared in the urine by 4 to 6 hours and one-half to one-third of the drug was excreted within 24 hours.

Amitriptyline is metabolized by N-demethylation and bridge hydroxylation in man, rabbit, and rat. Virtually the entire dose is excreted as glucuronide or sulfate conjugate of metabolites, with little unchanged drug appearing in the urine. Other metabolic pathways may be involved.

REFERENCES

Ayd, F.J., Jr.: Amitriptyline therapy for depressive reactions, Psychosom. *1*:320-325, Nov.-Dec. 1960.

Diamond, S.: Human metabolization of amitriptyline tagged with carbon 14, Curr. therap. Res. *7*:170-175, Mar. 1965.

Dorfman, W.: Clinical experiences with amitriptyline (A preliminary report), Psychosom. *1*:153-155, May-June 1960.

Falletta, J.M.; Stasney, C.R.; Mintz, A.A.: Amitriptyline poisoning treated with physostigmine, S. Med. J. *63*:1492-1493, Dec. 1970 (in Soc. Proc.)

Hollister, L.E.; Overall, J.E.; Johnson, M.; Pennington, V.; Katz, G.; Shelton, J.; Controlled comparison of amitriptyline, imipramine and placebo in hospitalized depressed patients, J. Nerv. and Ment. Dis. *139*:370-375, Oct. 1964.

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Hordern, A.; Burt, C.G.; Holt, N.F.: Depressive states. A pharmacotherapeutic study, Springfield, Ill., Charles C. Thomas, 1965.

Klerman, G.L.; Cole, J.O.; Clinical pharmacology of imipramine and related antidepressant compounds, Int. J. Psychiat *3*:267-304, Apr. 1967.

McConaghy, N.; Joffe, A.D.; Kingston, W.R.; Stevenson, H.G.; Atkinsion, I.; Cole, E.; Fennessy, L.A.; Correlation of clinical features of depressed out-patients with response to amitriptyline and protriptyline, Brit. J. Psychiat. *114*:103-106, Jan. 1968.

McDonald, I.M.; Perkins, M. Marjerrison, G.; Podilsky, M.: A controlled comparison of amitriptyline and electroconvulsive therapy in the treatment of depression, Amer. J. Psychiat. *122*:1427-1431, June 1966 (in Brief Communications).

Slovis, T.; Ott, J.; Teitelbaum, D.; Lipscomb, W.: Physostigmine therapy in acute tricyclic antidepressant poisoning, Clin. Toxicol. *4*:451-459, Sept. 1971.

Symposium on depression with special studies of a new antidepressant, amitriptyline, Dis. Nerv. Syst. *22*:5-56, May 1961 (Sect.2).

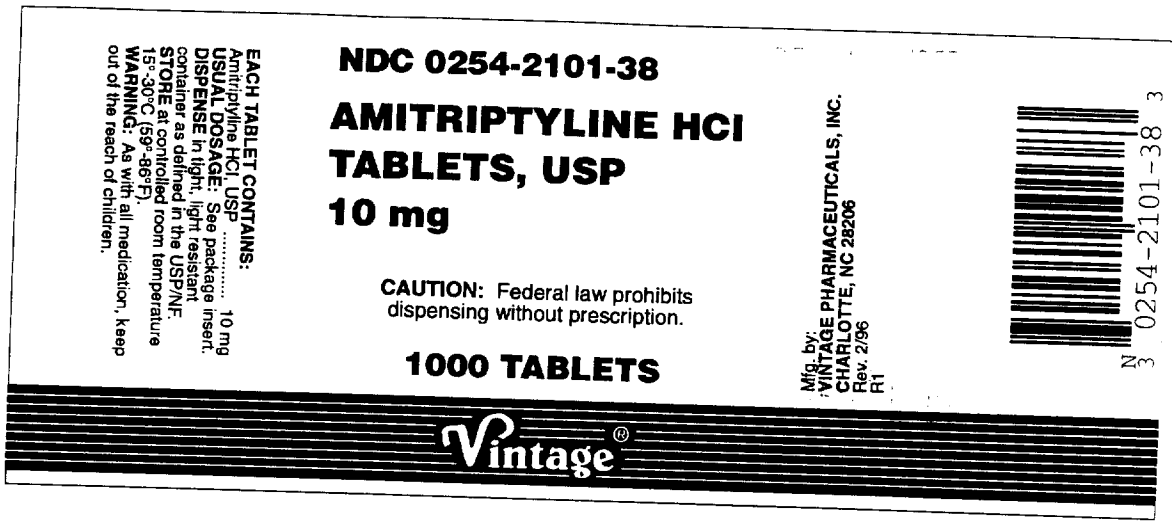
*Based on a maximum recommended amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50 kg patient.

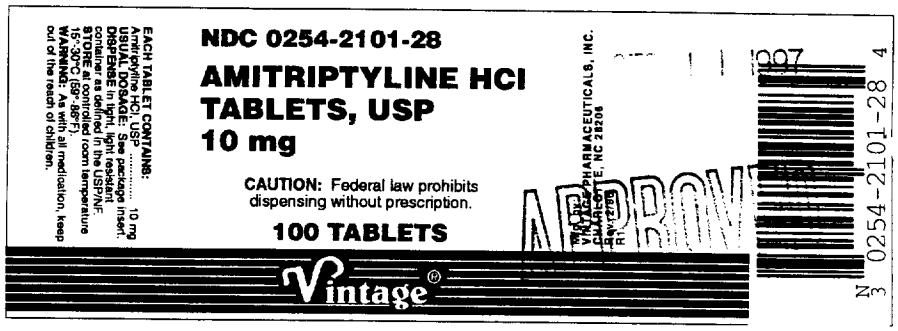
**Hollister, L.E.; JAMA 1979; *241*:2530-2533.

Manufactured by:
VINTAGE PHARMACEUTICALS, INC.
Charlotte, NC 28206

IN-117
Rev 6/97
R2

VINTAGE PHARMACEUTICALS, INC
Amitriptyline HCl Tablets,USP
10 mg

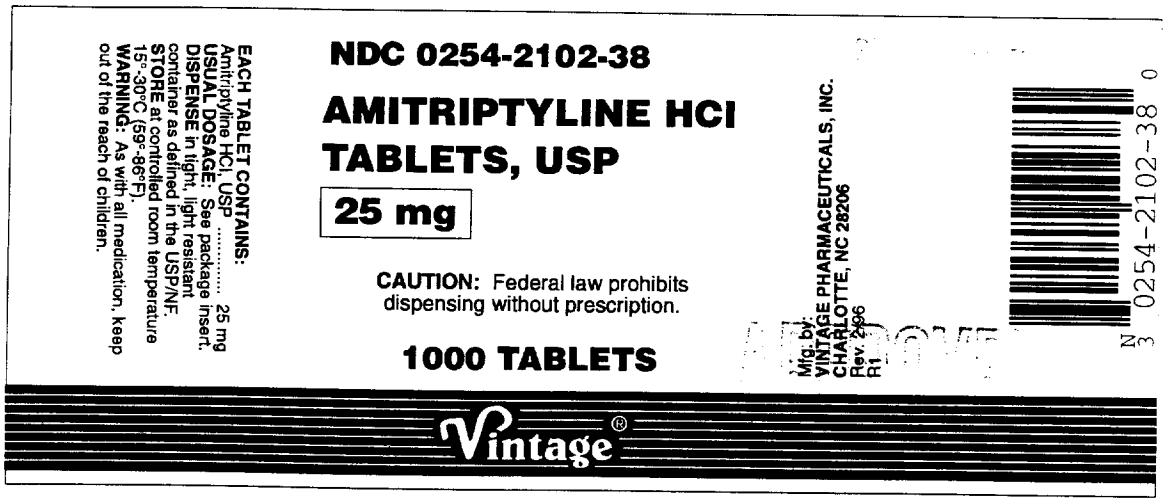




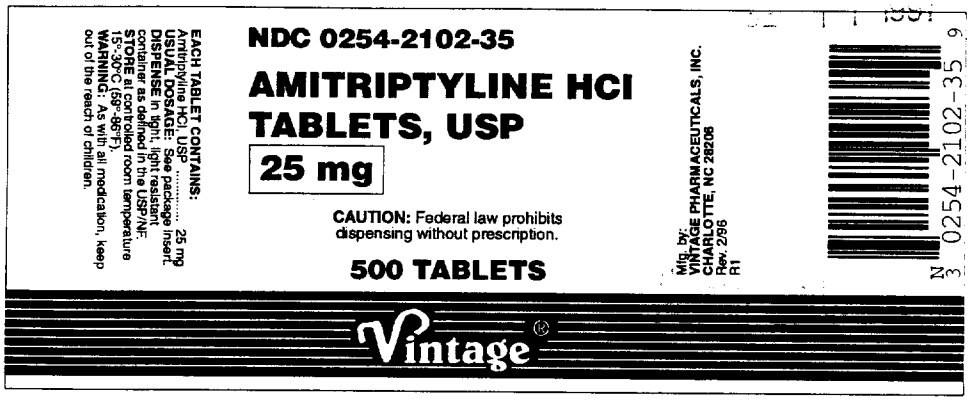
LABEL SIZE 1 5/8 X 4 5/8 INCHES

LABEL SIZE 2 X 5 INCHES

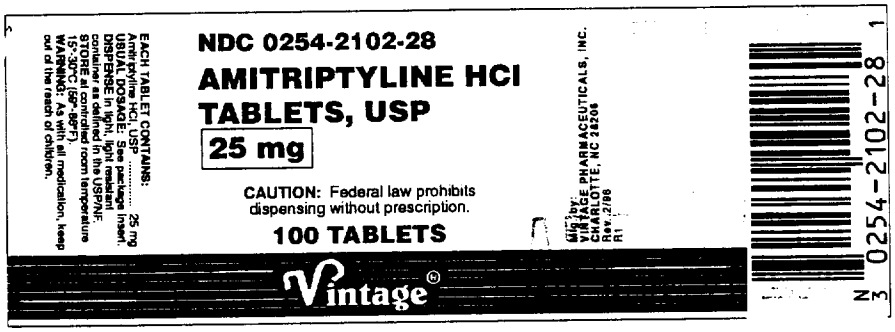
VINTAGE PHARMACEUTICALS, INC
Amitriptyline HCl Tablets,USP
25 mg



LABEL SIZE 2.5 X 6 INCHES

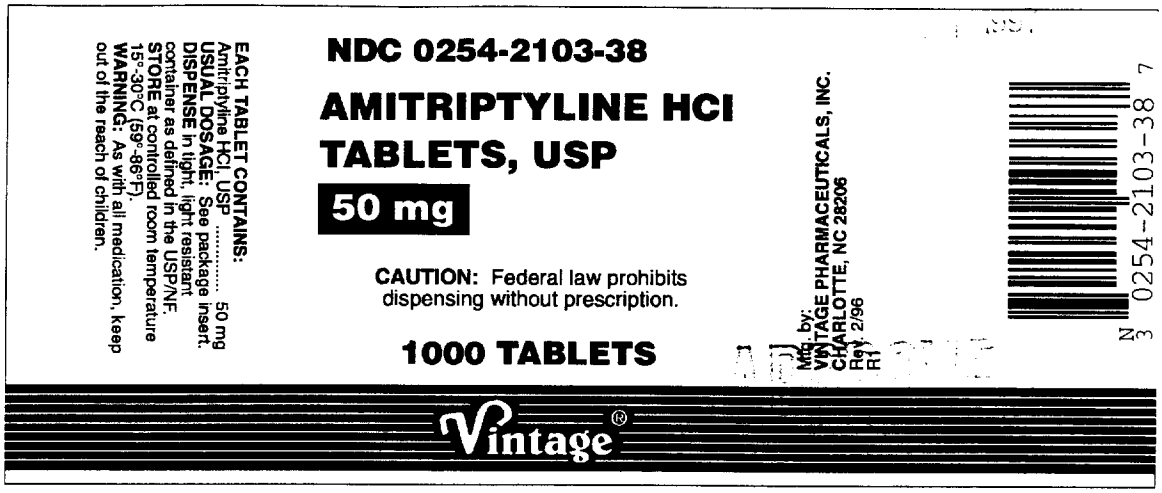


LABEL SIZE 2 X 5 INCHES



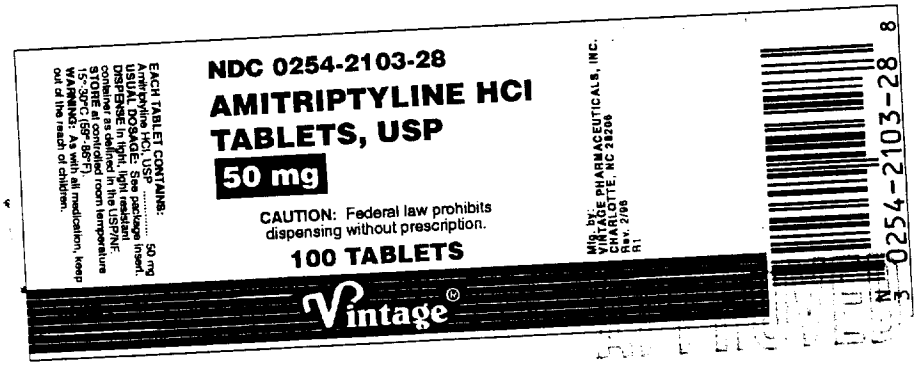
LABEL SIZE 1 5/8 X 4 5/8 INCHES

VINTAGE PHARMACEUTICALS, INC
Amitriptyline HCl Tablets,USP
50 mg



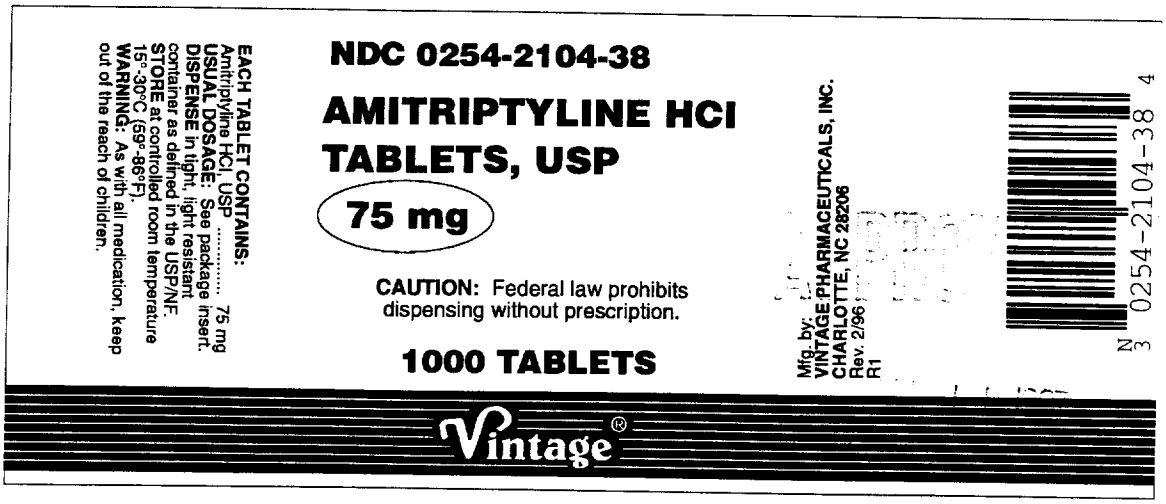
LABEL SIZE 2.5 X 6 INCHES

LABEL SIZE 2 X 5 INCHES

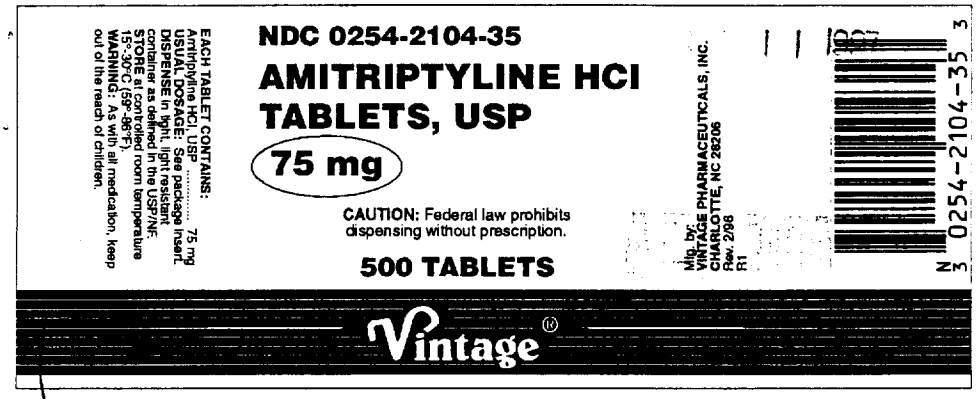


LABEL SIZE 1 5/8 X 4 5/8 INCHES

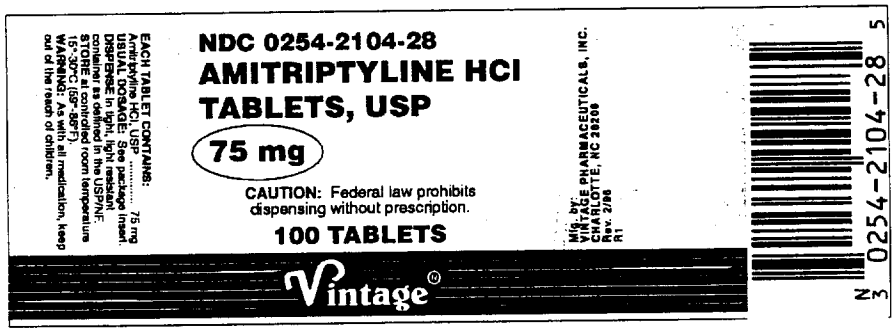
VINTAGE PHARMACEUTICALS, INC
Amitriptyline HCl Tablets,USP
75 mg



LABEL SIZE 2.5 X 6 INCHES

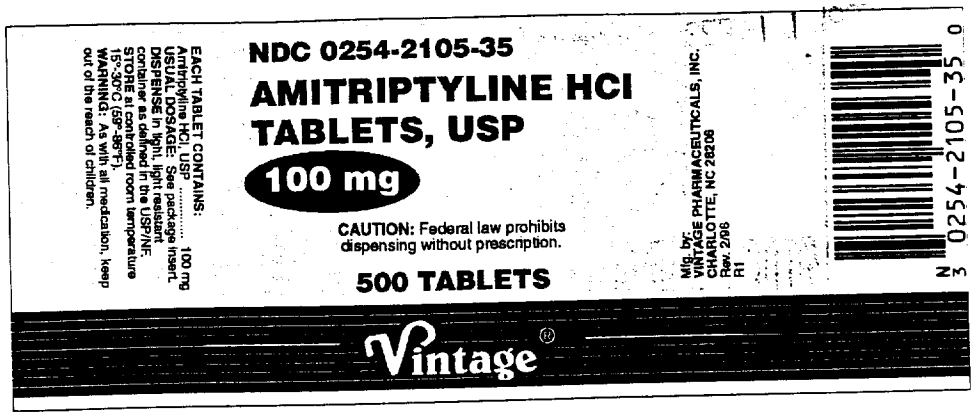


LABEL SIZE 2 X 5 INCHES



LABEL SIZE 1 5/8 X 4 5/8 INCHES

VINTAGE PHARMACEUTICALS, INC
Amitriptyline HCl Tablets, USP
100 mg



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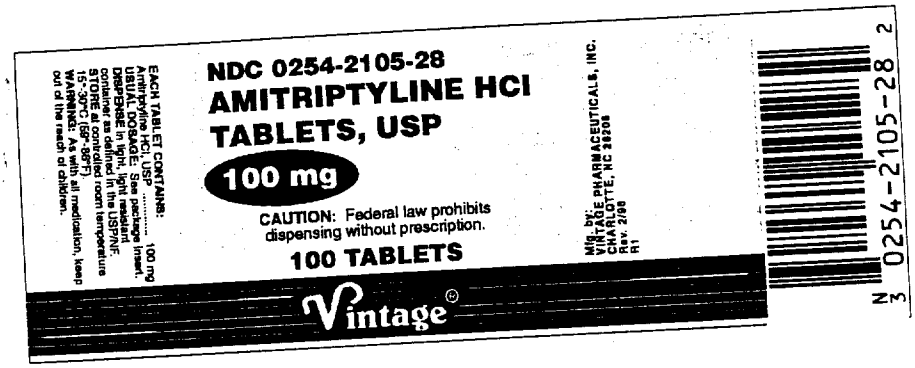
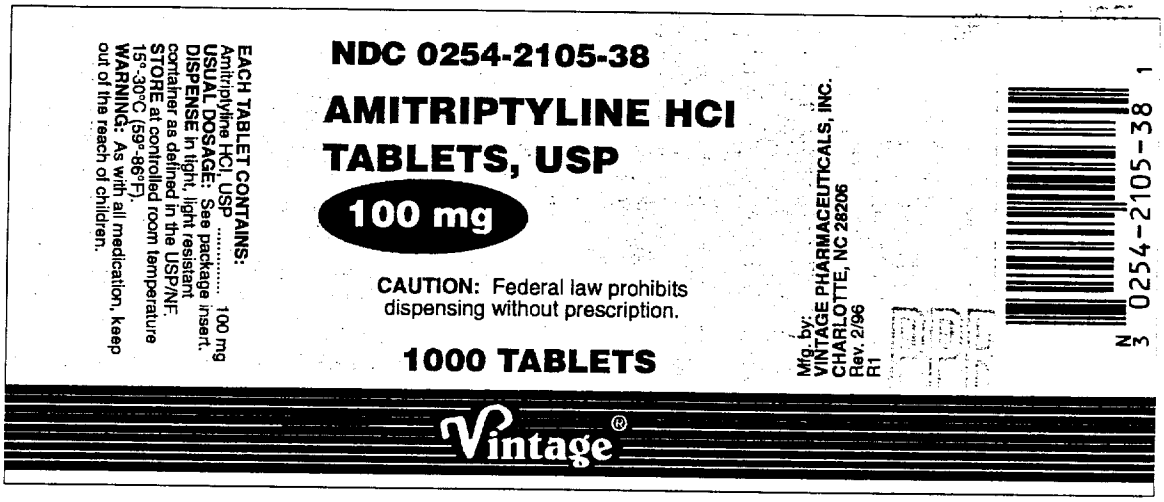


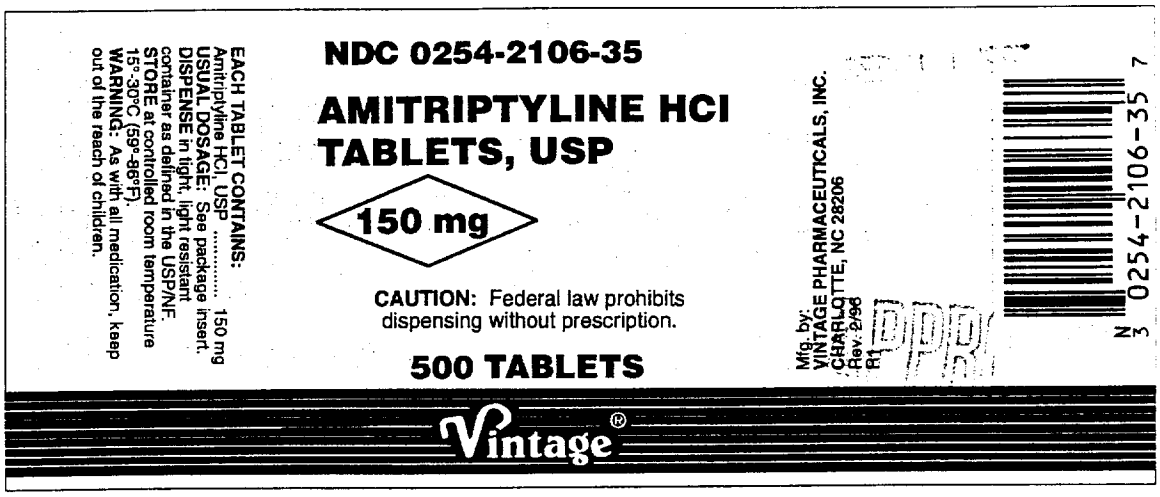
LABEL SIZE 1 5/8 X 4 5/8 INCHES

VINTAGE PHARMACEUTICALS, INC
Amitriptyline HCl Tablets, USP
100 mg

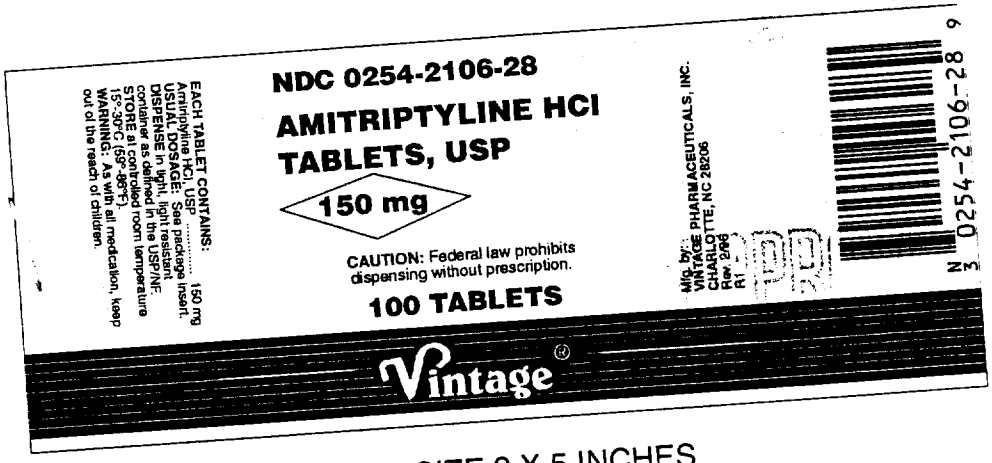


LABEL SIZE 2.5 X 6 INCHES

VINTAGE PHARMACEUTICALS, INC
Amitriptyline HCl Tablets, USP
150 mg



LABEL SIZE 2.5 X 6 INCHES



LABEL SIZE 2 X 5 INCHES

VINTAGE PHARMACEUTICALS, INC
Amitriptyline HCl Tablets, USP
150 mg

EACH TABLET CONTAINS:
Amitriptyline HCl, USP ..... 150 mg
USUAL DOSAGE: See package insert.
DISPENSE in tight, light resistant container as defined in the USP/NF.
STORE at controlled room temperature 15°-30°C (59°-86°F).
WARNING: As with all medication, keep out of the reach of children.

NDC 0254-2106-38

AMITRIPTYLINE HCl TABLETS, USP

150 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Mfg. by:
VINTAGE PHARMACEUTICALS, INC.
CHARLOTTE, NC 28206
Rev. 2/96
R1

N 3 0254-2106-38 8

Vintage®

LABEL SIZE 2.5 X 6 INCHES

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040218

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 2

2. ANDA **40-218**

3. NAME AND ADDRESS OF APPLICANT
Vintage Pharmaceuticals, Inc.
3241 Woodpark Boulevard
Charlotte, NC 28206

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of Zeneca's ELAVIL® (NDA 12-703). Patent certification and exclusivity statement are provided (Vol. 1.1, pp. 005-010).

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Amitriptyline Hydrochloride

7. PROPRIETARY NAME
Elavil®

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm		**FDA**	
Orig. submission	11/01/96	Acknowledgment letter	1/29/97
		CSO review	1/18/97
		Labeling review	3/11/97
		Bioequivalency review	4/30/97
		Deficiency facsimile	6/23/97
Amendment (FAX)	7/23/97		
Amendment (FAX)	8/28/97		

This review covers submission dated 7/23/97.

10. PHARMACOLOGICAL CATEGORY
Antidepressant - For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than are other depressive states.

11. Rx or OTC
℞

12. RELATED DMF(s)

(b)4 - Confidential Business

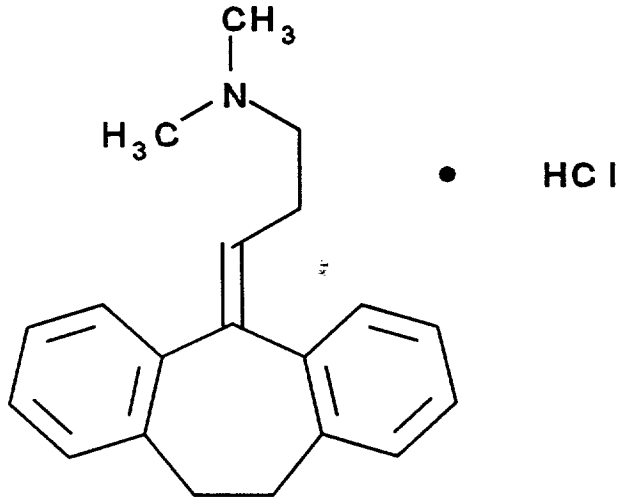
(b)4 - Confidential Business

13. DOSAGE FORM
Tablets **(Oral)**

14. STRENGTH(S)
10 mg, 25 mg, 50 mg, 75 mg, 100 mg and 150 mg

15. CHEMICAL NAME AND STRUCTURE

Amitriptyline Hydrochloride USP
$C_{20}H_{23}N.HCl$; M.W. = 313.87



10,11-Dihydro-*N*,*N*-dimethyl-5*H*-dibenzo[*a*,*d*]cycloheptene-$\Delta^{5,\gamma}$-propylamine hydrochloride. CAS [549-18-8]

Drug substance and drug product are official USP 23 items.

16. RECORDS AND REPORTS None

17. COMMENTS
   a. CMC deficiencies have been satisfactory addressed.
   b. Labeling is **satisfactory**, dated 8/11/97
   c. Bio review is **satisfactory**, dated 4/30/97.
   d. DMF [redacted]s **satisfactory**, dated 4/18/97
   e. Methods validation for drug substance and drug product **are not** required, both are compendial items.
   f. Establishment Evaluation Report is **acceptable**, dated 3/25/97.

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVE

19. REVIEWER: Raymond Brown

DATE COMPLETED: August 18, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040218

BIOEQUIVALENCE REVIEW(S)

ANDA 40-218

MAY 2 1997

Vintage Pharmaceuticals, Inc.
Attention: Rebecca Thurman
3241 Woodpark Blvd.
Charlotte NC 28206

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Amitriptyline Hydrochloride Tablets USP, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research