CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

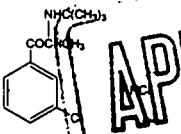
75491

DRAFT FINAL PRINTED LABELING

BUPROPION HYDROCHLORIDE TABLETS
75 mg and 100 mg

℞ only

DESCRIPTION: Bupropion hydrochloride, an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO{\cdot}HCl$. Bupropion hydrochloride powder is white or almost white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is as follows:



Bupropion Hydrochloride Tablets, for oral administration, are available containing 75 mg or 100 mg of bupropion hydrochloride. Each tablet also contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, crospovidone, hydrochloric acid, hydroxypropyl methylcellulose, microcrystalline cellulose, polydextrose, polyethylene glycol, stearic acid and titanium dioxide. In addition, the 75 mg tablets contain synthetic red iron oxide, synthetic yellow iron oxide and triacetin and the 100 mg tablets contain FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake and glyceryl triacetate.

CLINICAL PHARMACOLOGY: Pharmacodynamics and Pharmacological Actions: The neurochemical mechanism of the antidepressant effect of bupropion is not known. Bupropion does not inhibit monoamine oxidase. Compared to classical tricyclic antidepressants, it is a weak blocker of the neuronal uptake of serotonin and norepinephrine; it also inhibits the neuronal re-uptake of dopamine to some extent.

Bupropion produces dose-related CNS stimulant effects in animals, as evidenced by increased locomotor activity, increased rates of responding in various schedule-controlled operant behavior tasks, and, at high doses, induction of mild stereotyped behavior.

Bupropion causes convulsions in rodents and dogs at doses approximately tenfold the dose recommended as the human antidepressant dose.

Absorption, Distribution, Pharmacokinetics, Metabolism, and Elimination: ***Oral Bioavailability and Single-Dose Pharmacokinetics:*** In humans, following oral administration of bupropion, peak plasma bupropion concentrations are usually achieved within 2 hours, followed by a biphasic decline. The average half-life of the second (post-distributional) phase is approximately 14 hours, with a range of 8 to 24 hours. Six hours after a single dose, plasma bupropion concentrations are approximately 30% of peak concentrations. Plasma bupropion concentrations are dose-proportional following single doses of 100 to 250 mg; however, it is not known if the proportionality between dose and plasma level is maintained in chronic use.

The absolute bioavailability of bupropion tablets in humans has not been determined because an intravenous formulation for human use is not available.

However, it appears likely that only a small proportion of any orally administered dose reaches the systemic circulation intact. For example, the absolute bioavailability of bupropion in animals (rats and dogs) ranges from 5% to 20%.

Metabolism: Following oral administration of 200 mg of ^{14}C-bupropion, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding documenting the extensive metabolism of bupropion.

Several of the known metabolites of bupropion are pharmacologically active, but their potency and toxicity relative to bupropion have not been fully characterized. However, because of their longer elimination half-lives, the plasma concentrations of at least two of the known metabolites can be expected, especially in chronic use, to be very much higher than the plasma concentration of bupropion. This is of potential clinical importance because factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure, age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of these active metabolites.

Furthermore, bupropion has been shown to induce its own metabolism in three animal species (mice, rats, and dogs) following subchronic administration. If induction also occurs in humans, the relative contribution of bupropion and its metabolites to the clinical effects of bupropion may be changed in chronic use.

Plasma and urinary metabolites so far identified include biotransformation products formed via reduction of the carbonyl group and/or hydroxylation of the *tert*-butyl group of bupropion. Four basic metabolites have been identified.

They are the *erythro*- and *threo*-amino alcohols of bupropion, the *erythro*-amino diol of bupropion, and a morpholinol metabolite (formed from hydroxylation of the *tert*-butyl group of bupropion).

The morpholinol metabolite appears in the systemic circulation almost as rapidly as the parent drug following a single oral dose. Its peak level is three times the peak level of the parent drug; it has a half-life on the order of 24 hours; and its AUC 0 to 60 hours is about 15 times that of bupropion.

The *threo*-amino alcohol metabolite has a plasma concentration-time profile similar to that of the morpholinol metabolite. The *erythro*-amino alcohol and the *erythro*-amino diol metabolites generally cannot be detected in the systemic circulation following a single oral dose of the parent drug. The morpholinol and the *threo*-amino alcohol metabolites have been found to be half as potent as bupropion in animal screening tests for antidepressant drugs.

During a chronic dosing study in 14 depressed patients with left ventricular dysfunction, it was found that there was substantial interpatient variability (two- to fivefold) in the trough steady-state concentrations of bupropion and the morpholinol and *threo*-amino alcohol metabolites. In addition, the steady-state plasma concentrations of these metabolites were 10 to 100 times the steady-state concentrations of the parent drug.

The effect of other disease states and altered organ function on the metabolism and/or elimination of bupropion has not been studied in detail. However, the elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo conjugation in the liver prior to urinary excretion. The preliminary results of a comparative single-dose pharmacokinetic study in normal versus cirrhotic patients indicated that half-lives of the metabolites were prolonged by cirrhosis and that the metabolites accumulated to levels two to three times those in normals.

The effect of age on plasma concentrations of bupropion and its metabolites has not been characterized.

In vitro tests show that bupropion is 80% or more bound to human albumin at plasma concentrations up to 800 micromolar (200 mcg/mL).

INDICATIONS AND USAGE: Bupropion Hydrochloride Tablets are indicated for the treatment of depression. A physician considering bupropion for the management of a patient's first episode of depression should be aware that the drug may cause generalized seizures in a dose-dependent manner with an approximate incidence of 0.4% (4/1000). This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted (see WARNINGS).

The efficacy of bupropion has been established in three placebo-controlled trials, including two of approximately 3-weeks duration in depressed inpatients, and one of approximately 6-weeks duration in depressed outpatients. The depression studied in the patients studied corresponds most closely to the Major Depressive Disorder of the APA Diagnostic and Statistical Manual III.

Major depression implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least two weeks); it should include at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased irritability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

Effectiveness of bupropion in long-term use, that is, for more than 6-weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use bupropion for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: Bupropion is contraindicated in patients with a seizure disorder. Bupropion is contraindicated in patients treated with ZYBAN™ (bupropion hydrochloride) Sustained-Release Tablets, or any other medications that contain bupropion because the incidence of seizure is dose dependent. Bupropion is also contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in such patients treated with bupropion. The concurrent administration of bupropion and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion. Bupropion is contraindicated in patients who have shown an allergic response to it.

WARNINGS: Patients should be made aware that bupropion hydrochloride tablets contain the same active ingredient found in ZYBAN™, used as an aid to smoking cessation treatment, and that bupropion hydrochloride should not be used in combination with ZYBAN™, or any other medications that contain bupropion.

Seizures: Bupropion hydrochloride is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for bupropion hydrochloride increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the initial development, 25 among approximately 2400 patients treated with bupropion hydrochloride experienced seizures. At the time of seizure, seven patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (8/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8-week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight seizures occurred during the initial 8-week treatment period and five seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

Recommendations for Reducing the Risk of Seizure: **Retrospective analysis of clinical experience gained during the development of bupropion hydrochloride suggests that the risk of seizure may be minimized if (1) the total daily dose of bupropion hydrochloride does *not* exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose *not* to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when bupropion is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.**

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

PRECAUTIONS: General: ***Agitation and Insomnia:*** A substantial proportion of patients treated with bupropion experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of treatment with bupropion.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with bupropion. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Bupropion is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 28% of patients receiving bupropion. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with bupropion did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of bupropion should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for bupropion should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: There is no clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants.

Because bupropion and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients: Patients should be made aware that bupropion contains the same active ingredient found in ZYBAN™, used as an aid to smoking cessation treatment, and that bupropion hydrochloride should not be used in combination with ZYBAN™, or any other medications that contain bupropion.

Physicians are advised to discuss the following issues with patients:

Patients should be instructed to take bupropion in equally divided doses three or four times a day to minimize the risk of seizure.

Patients should be told that any CNS-active drug like bupropion may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that bupropion does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the use and cessation of use of alcohol may alter the seizure threshold, and, therefore, that the consumption of alcohol should be minimized, and, if possible, avoided completely.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs. Concern is warranted because bupropion and other drugs may affect each other's metabolism.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of bupropion and other drugs.

However, animal data suggest that bupropion may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug-metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of bupropion and L-dopa. Administration of bupropion to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of bupropion and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2 to 3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

Pregnancy: *Teratogenic Effects. Pregnancy Category B:* Reproduction studies have been performed in rabbits and rats at doses up to 15 to 45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality.) There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of bupropion on labor and delivery in humans is unknown.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from bupropion, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of bupropion in individuals under 18 years old have not been established.

Use in the Elderly: Bupropion has not been systematically evaluated in older patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS.) Adverse events commonly encountered in patients treated with bupropion are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of treatment with bupropion in approximately 10% of the 2400 patients and volunteers who participated in clinical trials during the product's initial development. The more common events causing discontinuation include neuropsychiatric disturbances (3%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. Consequently, the table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of bupropion hydrochloride under relatively similar conditions of daily dosage (300 to 600 mg), setting, and duration (3 to 4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of bupropion is provided in the WARNINGS and PRECAUTIONS sections.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	Bupropion Patients (n=323)	Placebo Patients (n=185)
CARDIOVASCULAR		
Cardiac Arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	8.0	6.5
GASTROINTESTINAL		
Anorexia	18.3	18.4
Appetite Increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/Vomiting	22.9	18.9
Weight Gain	13.6	22.7
Weight Loss	23.2	23.2
GENITOURINARY		
Impotence	3.4	3.1
Menstrual Complaints	4.7	1.1
Urinary Frequency	2.5	2.2
Urinary Retention	1.9	2.2
MUSCULOSKELETAL		
Arthritis	3.1	2.7
NEUROLOGICAL		
Akathisia	1.5	1.1
Akinesia/Bradykinesia	8.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	22.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	18.6	15.7
Muscle Spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory Disturbance	4.0	3.2
Tremor	21.1	7.6
NEUROPSYCHIATRIC		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased Libido	3.1	1.6
Delusions	1.2	1.1
Disturbed Concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
NONSPECIFIC		
Fatigue	5.0	8.6
Fever/Chills	1.2	0.5
RESPIRATORY		
Upper Respiratory Complaints	5.0	11.4
SPECIAL SENSES		
Auditory Disturbances	5.3	3.2
Blurred Vision	14.6	10.3
Gustatory Disturbance	3.1	1.1

*Events reported by at least 1% of patients receiving bupropion are included.

Other Events Observed During the Development of Bupropion: The conditions and duration of exposure to bupropion varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by bupropion. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; rare were flushing, pallor, phlebitis, and myocardial infarction.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color, hirsutism, and acne.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and fecal impaction/jaundice; rare were rectal complaints, colitis, G.I. bleeding, intestinal perforation, and stomach ulcer.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare were lymphadenopathy, anemia, and pancytopenia.

Musculoskeletal: Rare was musculoskeletal chest pain.

Neurological: (See WARNINGS.) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; rare were EEG abnormality, abnormal neurological exam, impaired attention, sciatica, and aphasia.

Neuropsychiatric: (See PRECAUTIONS.) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis, rate or rhythm disorder, pneumonia, and pulmonary embolism.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction, and overdose.

Postintroduction Reports: Voluntary reports of adverse events temporally associated with bupropion that have been received since market introduction and which may have no causal relationship with the drug include the following:

Cardiovascular: orthostatic hypotension, third degree heart block

Endocrine: syndrome of inappropriate antidiuretic hormone secretion

Gastrointestinal: esophagitis, hepatitis

Hemic And Lymphatic: ecchymosis, leukocytosis, leukopenia

Musculoskeletal: arthralgia, myalgia, muscle rigidity/fever/rhabdomyolysis

Nervous: coma, delirium, dream abnormalities, paresthesia, unmasking of tardive dyskinesia

Skin and Appendages: Stevens-Johnson syndrome, angioedema, exfoliative dermatitis, urticaria

Special Senses: tinnitus

DRUG ABUSE AND DEPENDENCE: Humans: Controlled clinical studies conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement.

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg bupropion hydrochloride produced mild amphetamine-like activity as compared to placebo on the morphine-benzedrine subscale of the Addiction Research Center Index (ARCI) and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.

Findings in clinical trials, however, are not known to predict the abuse potential of drugs reliably. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be especially reinforcing to amphetamine or stimulant abusers. However, higher doses, which could not be tested because of the risk of seizure, might be modestly attractive to those who abuse stimulant drugs.

Animals: Studies in rodents have shown that bupropion exhibits some pharmacologic actions common to psychostimulants, including increases in locomotor activity and the production of a mild stereotyped behavior and increases in rates of responding in several schedule-controlled behavior paradigms. Drug discrimination studies in rats showed stimulus generalization between bupropion and amphetamine and other psychostimulants. Rhesus monkeys have been shown to self-administer bupropion intravenously.

OVERDOSAGE: Lethal Doses in Animals: In rats, the acute oral LD_{50} values were 607 mg/kg (males) and 482 mg/kg (females). Respective values for mice were 544 mg/kg and 636 mg/kg. Signs of acute toxicity included labored breathing, salivation, arched back, ptosis, ataxia, and convulsions.

Human Overdose Experience: There has been limited clinical experience with overdosage of bupropion hydrochloride. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of bupropion hydrochloride and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

Since introduction, overdoses of bupropion hydrochloride up to 17,500 mg have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, and tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported rarely in patients ingesting massive doses of bupropion. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

Management of Overdose: Following suspected overdose, hospitalization is advised. If the patient is conscious, vomiting should be induced by s ipecac. Activated charcoal also may be administered every 6 hours du first 12 hours after ingestion. Baseline laboratory values should be o Electrocardiogram and EEG monitoring also are recommended for the hours. Adequate fluid intake should be provided.

If the patient is stuporous, comatose, or convulsing, airway intut recommended prior to undertaking gastric lavage. Although there is lit cal experience with lavage following an overdose of bupropion, it is lik of benefit within the first 12 hours after ingestion since absorption of t may not yet be complete.

While diuresis, dialysis, or hemoperfusion are sometimes used to tr overdosage, there is no experience with their use in the management doses of bupropion. Because diffusion of bupropion from tissue to may be slow, dialysis may be of minimal benefit several hours after ove

Based on studies in animals, it is recommended that seizures be with an intravenous benzodiazepine preparation and other supportiv sures, as appropriate.

Further information about the treatment of overdoses may be avail from a poison control center.

DOSAGE AND ADMINISTRATION: General Dosing Considerations: It is ularly important to administer bupropion hydrochloride in a manner mo to minimize the risk of seizure (see WARNINGS). Increases in dose sho exceed 100 mg/day in a 3-day period. Gradual escalation in dosage is i portant if agitation, motor restlessness, and insomnia, often seen du initial days of treatment, are to be minimized. If necessary, these effe be managed by temporary reduction of dose or the short-term adminis of an intermediate to long-acting sedative hypnotic. A sedative hypnotic is not required beyond the first week of treatment. Insomnia may also b mized by avoiding bedtime doses. If distressing, untoward effects sup dose escalation should be stopped.

No single dose of bupropion hydrochloride tablet should exceed 1 Bupropion should be administered t.i.d., preferably with at least 6 ho tween successive doses.

Usual Dosage For Adults: The usual adult dose is 300 mg/day, give Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on response, this dose may be increased to 300 mg/day, given as 100 m no sooner than 3 days after beginning therapy (see table below).

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets: Morning	Midday	E
1	200 mg	100 mg	1	0	
4	300 mg	100 mg	1	1	

Increasing the Dosage Above 300 mg/Day: As with other antidepressa full antidepressant effect of bupropion hydrochloride may not be eviden weeks of treatment or longer. An increase in dosage, up to a maxir 450 mg/day, given in divided doses of not more than 150 mg each, considered for patients in whom no clinical improvement is noted after weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be plished using the 75 or 100 mg tablets. The 100 mg tablet must be a tered q.i.d. with at least 4 hours between successive doses, in order exceed the limit of 150 mg in a single dose. Bupropion hydrochloride be discontinued in patients who do not demonstrate an adequate re after an appropriate period of treatment at 450 mg/day.

Elderly Patients: In general, older patients are known to metabolize more slowly and to be more sensitive to the anticholinergic, sedative, a diovascular side effects of antidepressant drugs. Clinical trials enrolled hundred patients 60 years of age and older. The experience with these p and younger ones was similar.

Maintenance: The lowest dose that maintains remission is recomm Although it is not known how long the patient should remain on bupro is generally recognized that acute episodes of depression require months or longer of antidepressant drug treatment.

HOW SUPPLIED: Bupropion Hydrochloride Tablets are available con 75 mg or 100 mg of bupropion hydrochloride.

The 75 mg tablets are peach, film-coated, round, unscored, bic beveled edge tablets debossed with **M** on one side of the tablet and 4 the other side. They are available as follows:

NDC 0378-0433-01
bottles of 100 tablets
NDC 0378-0433-05
bottles of 500 tablets

The 100 mg tablets are light blue, film-coated, round, unscored, bic beveled edge tablets debossed with **M** on one side of the tablet and the other side. They are available as follows:

NDC 0378-0435-01
bottles of 100 tablets
NDC 0378-0435-05
bottles of 500 tablets

STORE AT ROOM TEMPERATURE 15° TO 25°C (59° TO 77°F).
PROTECT FROM MOISTURE.

Dispense in a tight, light-resistant container as defined in the USP w child-resistant closure.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

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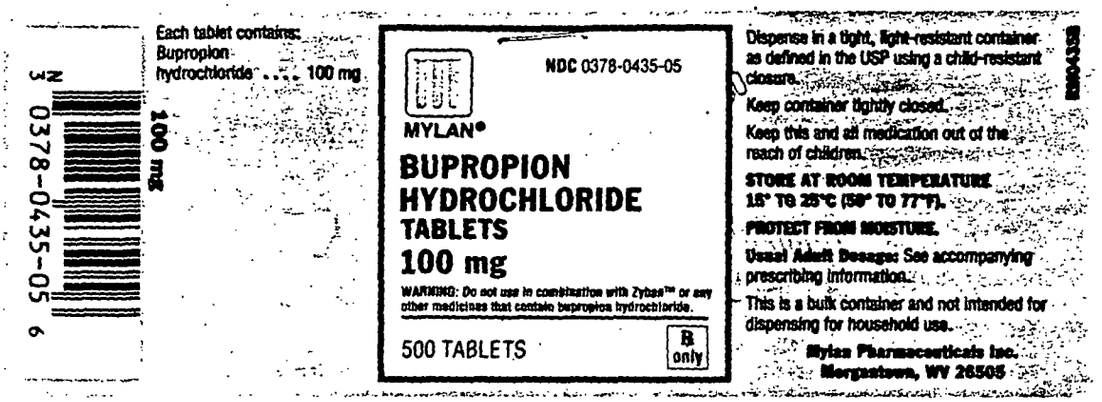
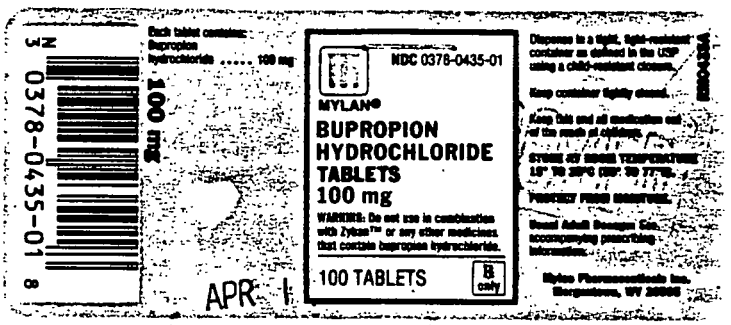

Each tablet contains:
Bupropion hydrochloride . . . . 100 mg
100 mg
N 3 0378-0435-05 6
NDC 0378-0435-05
MYLAN®
BUPROPION HYDROCHLORIDE
TABLETS
100 mg
WARNING: Do not use in combination with Zyban™ or any other medicines that contain bupropion hydrochloride.
500 TABLETS
℞ only
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT ROOM TEMPERATURE 15° TO 25°C (59° TO 77°F).
PROTECT FROM MOISTURE.
Usual Adult Dosage: See accompanying prescribing information.
This is a bulk container and not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505


N 0 0378-0435-01 8
100 mg
APR
MDC 0378-0435-01
MYLAN®
BUPROPION HYDROCHLORIDE TABLETS
100 mg
100 TABLETS
Rx only

Each tablet contains:
Bupropion
hydrochloride ..... 75 mg

NDC 0378-0433-05

MYLAN®

BUPROPION HYDROCHLORIDE TABLETS 75 mg

WARNING: Do not use in combination with Zyban™ or any other medicines that contain bupropion hydrochloride.

500 TABLETS

℞ only

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT ROOM TEMPERATURE 15° TO 25°C (59° TO 77°F).

PROTECT FROM MOISTURE.

Usual Adult Dosage: See accompanying prescribing information.

This is a bulk container and not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

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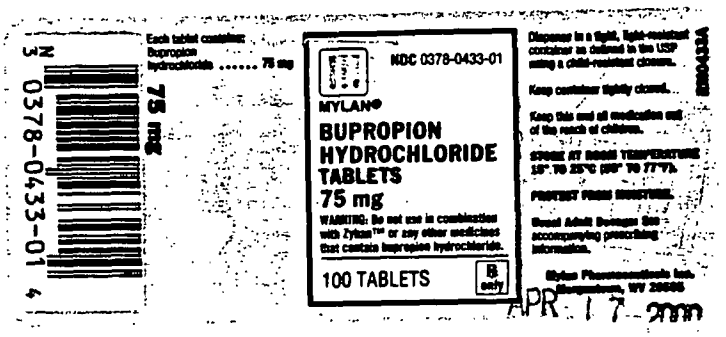
Each tablet contains:
Bupropion
hydrochloride ..... 75 mg
75 mg
NDC 0378-0433-01
MYLAN®
BUPROPION
HYDROCHLORIDE
TABLETS
75 mg
WARNING: Do not use in combination
with Zyban™ or any other medicines
that contain bupropion hydrochloride.
100 TABLETS
Rx only
Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out
of the reach of children.
PROTECT FROM MOISTURE.
Read Adult Dosage and
accompanying prescribing
information.
APR 17 2000