

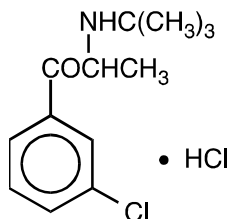
1 **PRESCRIBING INFORMATION**

2 **WELLBUTRIN[®]**
3 **(bupropion hydrochloride)**
4 **Tablets**

5
6 **“Patient Information” enclosed**

7 **DESCRIPTION**

8 WELLBUTRIN (bupropion hydrochloride), an antidepressant of the aminoketone class, is
9 chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other
10 known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related
11 to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-
12 propanone hydrochloride. The molecular weight is 276.2. The empirical formula is
13 C₁₃H₁₈ClNO•HCl. Bupropion hydrochloride powder is white, crystalline, and highly soluble in
14 water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The
15 structural formula is:



17
18
19 WELLBUTRIN is supplied for oral administration as 75-mg (yellow-gold) and 100-mg (red)
20 film-coated tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the
21 inactive ingredients: 75-mg tablet – D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake,
22 hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose,
23 polyethylene glycol, talc, and titanium dioxide; 100-mg tablet FD&C Red No. 40 Lake, FD&C
24 Yellow No. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline
25 cellulose, polyethylene glycol, talc, and titanium dioxide.

26 **CLINICAL PHARMACOLOGY**

27 **Pharmacodynamics:** The neurochemical mechanism of the antidepressant effect of
28 bupropion is not known. Bupropion is a relatively weak inhibitor of the neuronal uptake of
29 norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase.

30 Bupropion produces dose-related central nervous system (CNS) stimulant effects in animals,
31 as evidenced by increased locomotor activity, increased rates of responding in various
32 schedule-controlled operant behavior tasks, and, at high doses, induction of mild stereotyped
33 behavior.

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

3 **Pharmacokinetics:** Bupropion is a racemic mixture. The pharmacological activity and
4 pharmacokinetics of the individual enantiomers have not been studied. In humans, following oral
5 administration of WELLBUTRIN, peak plasma bupropion concentrations are usually achieved
6 within 2 hours, followed by a biphasic decline. The terminal phase has a mean half-life of
7 14 hours, with a range of 8 to 24 hours. The distribution phase has a mean half-life of 3 to
8 4 hours. The mean elimination half-life (\pm SD) of bupropion after chronic dosing is 21 (\pm 9)
9 hours, and steady-state plasma concentrations of bupropion are reached within 8 days. Plasma
10 bupropion concentrations are dose-proportional following single doses of 100 to 250 mg;
11 however, it is not known if the proportionality between dose and plasma level is maintained in
12 chronic use.

13 **Absorption:** The absolute bioavailability of WELLBUTRIN Tablets in humans has not been
14 determined because an intravenous formulation for human use is not available. However, it
15 appears likely that only a small proportion of any orally administered dose reaches the systemic
16 circulation intact.

17 **Distribution:** In vitro tests show that bupropion is 84% bound to human plasma protein at
18 concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion
19 metabolite is similar to that for bupropion, whereas the extent of protein binding of the
20 threohydrobupropion metabolite is about half that seen with bupropion.

21 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have been
22 shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group
23 of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion,
24 which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome
25 P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion,
26 while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.
27 Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-
28 chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and
29 toxicity of the metabolites relative to bupropion have not been fully characterized. However, it
30 has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one
31 half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold
32 less potent than bupropion. This may be of clinical importance because their plasma
33 concentrations are as high or higher than those of bupropion.

34 Because bupropion is extensively metabolized, there is the potential for drug-drug
35 interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6
36 (CYP2B6) isoenzyme. Although bupropion is not metabolized by cytochrome P450IID6
37 (CYP2D6), there is the potential for drug-drug interactions when bupropion is co-administered
38 with drugs metabolized by this isoenzyme (see PRECAUTIONS: Drug Interactions).

39 Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur
40 approximately 3 hours after administration of WELLBUTRIN Tablets. Peak plasma

1 concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug
2 at steady state. The elimination half-life of hydroxybupropion is approximately 20 (\pm 5) hours,
3 and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations
4 for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the
5 hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (\pm 10) and
6 37 (\pm 13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion,
7 respectively.

8 Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300
9 to 450 mg/day.

10 **Elimination:** Following oral administration of 200 mg of 14 C-bupropion in humans, 87% and
11 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the
12 fraction of the oral dose of WELLBUTRIN excreted unchanged was only 0.5%, a finding
13 consistent with the extensive metabolism of bupropion.

14 **Populations Subgroups:** Factors or conditions altering metabolic capacity (e.g., liver
15 disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may
16 be expected to influence the degree and extent of accumulation of the active metabolites of
17 bupropion. The elimination of the major metabolites of bupropion may be affected by reduced
18 renal or hepatic function because they are moderately polar compounds and are likely to undergo
19 further metabolism or conjugation in the liver prior to urinary excretion.

20 **Hepatic:** The effect of hepatic impairment on the pharmacokinetics of bupropion was
21 characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in
22 patients with mild to severe cirrhosis. The first study showed that the half-life of
23 hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in
24 8 healthy volunteers (32 \pm 14 hours versus 21 \pm 5 hours, respectively). Although not statistically
25 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be
26 greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life
27 for bupropion and the other metabolites in the 2 patient groups were minimal.

28 The second study showed that there were no statistically significant differences in the
29 pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate
30 hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in
31 some of the pharmacokinetic parameters for bupropion (AUC, C_{max} , and T_{max}) and its active
32 metabolites ($t_{1/2}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with
33 severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean
34 difference: by approximately 70% and 3-fold, respectively) and more variable when compared to
35 values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients
36 with severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite
37 hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-
38 alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was
39 approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion
40 and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours

1 later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean
2 half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold,
3 respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see
4 WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

5 **Renal:** The effect of renal disease on the pharmacokinetics of bupropion has not been
6 studied. The elimination of the major metabolites of bupropion may be affected by reduced renal
7 function.

8 **Left Ventricular Dysfunction:** During a chronic dosing study in 14 depressed patients
9 with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), no apparent
10 effect on the pharmacokinetics of bupropion or its metabolites was revealed, compared to healthy
11 volunteers.

12 **Age:** The effects of age on the pharmacokinetics of bupropion and its metabolites have not
13 been fully characterized, but an exploration of steady-state bupropion concentrations from
14 several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on
15 a 3 times daily schedule, revealed no relationship between age (18 to 83 years) and plasma
16 concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the
17 disposition of bupropion and its metabolites in elderly subjects was similar to that of younger
18 subjects. These data suggest there is no prominent effect of age on bupropion concentration;
19 however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly
20 are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS:
21 Geriatric Use).

22 **Gender:** A single-dose study involving 12 healthy male and 12 healthy female volunteers
23 revealed no sex-related differences in the pharmacokinetic parameters of bupropion.

24 **Smokers:** The effects of cigarette smoking on the pharmacokinetics of bupropion were
25 studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17
26 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there
27 were no statistically significant differences in C_{max} , half-life, T_{max} , AUC or clearance of
28 bupropion or its active metabolites between smokers and nonsmokers.

29 **INDICATIONS AND USAGE**

30 WELLBUTRIN is indicated for the treatment of depression. A physician considering
31 WELLBUTRIN for the management of a patient's first episode of depression should be aware
32 that the drug may cause generalized seizures in a dose-dependent manner with an approximate
33 incidence of 0.4% (4/1,000). This incidence of seizures may exceed that of other marketed
34 antidepressants by as much as 4-fold. This relative risk is only an approximate estimate because
35 no direct comparative studies have been conducted (see WARNINGS).

36 The efficacy of WELLBUTRIN has been established in 3 placebo-controlled trials, including
37 2 of approximately 3 weeks' duration in depressed inpatients and one of approximately 6 weeks'
38 duration in depressed outpatients. The depressive disorder of the patients studied corresponds
39 most closely to the Major Depression category of the APA Diagnostic and Statistical Manual III.

1 Major Depression implies a prominent and relatively persistent depressed or dysphoric mood
2 that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should
3 include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor
4 agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased
5 fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and
6 suicidal ideation or attempts.

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

11 **CONTRAINDICATIONS**

12 WELLBUTRIN is contraindicated in patients with a seizure disorder.

13 WELLBUTRIN is contraindicated in patients treated with ZYBAN[®] (bupropion
14 hydrochloride) Sustained-Release Tablets, or any other medications that contain bupropion
15 because the incidence of seizure is dose dependent.

16 WELLBUTRIN is also contraindicated in patients with a current or prior diagnosis of bulimia
17 or anorexia nervosa because of a higher incidence of seizures noted in such patients treated with
18 WELLBUTRIN.

19 WELLBUTRIN is contraindicated in patients undergoing abrupt discontinuation of alcohol or
20 sedatives (including benzodiazepines).

21 The concurrent administration of WELLBUTRIN and a monoamine oxidase (MAO) inhibitor
22 is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor
23 and initiation of treatment with WELLBUTRIN.

24 WELLBUTRIN is contraindicated in patients who have shown an allergic response to
25 bupropion or the other ingredients that make up WELLBUTRIN Tablets.

26 **WARNINGS**

27 **Patients should be made aware that WELLBUTRIN contains the same active ingredient**
28 **found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN**
29 **should not be used in combination with ZYBAN, or any other medications that contain**
30 **bupropion.**

31 **Seizures:** Bupropion is associated with seizures in approximately 0.4% (4/1,000) of
32 patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of
33 other marketed antidepressants by as much as 4-fold. This relative risk is only an
34 approximate estimate because no direct comparative studies have been conducted. The
35 estimated seizure incidence for WELLBUTRIN increases almost tenfold between 450 and
36 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third
37 the maximum recommended daily dose (450 mg). Given the wide variability among
38 individuals and their capacity to metabolize and eliminate drugs this disproportionate
39 increase in seizure incidence with dose incrementation calls for caution in dosing.

1 During the initial development, 25 among approximately 2,400 patients treated with
2 WELLBUTRIN experienced seizures. At the time of seizure, 7 patients were receiving daily
3 doses of 450 mg or below for an incidence of 0.33% (3/1,000) within the recommended dose
4 range. Twelve patients experienced seizures at 600 mg/day (2.3% incidence); 6 additional
5 patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

6 A separate, prospective study was conducted to determine the incidence of seizure
7 during an 8-week treatment exposure in approximately 3,200 additional patients who
8 received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond
9 8 weeks if clinically indicated. Eight seizures occurred during the initial 8-week treatment
10 period and 5 seizures were reported in patients continuing treatment beyond 8 weeks,
11 resulting in a total seizure incidence of 0.4%.

12 The risk of seizure appears to be strongly associated with dose. Sudden and large
13 increments in dose may contribute to increased risk. While many seizures occurred early in
14 the course of treatment, some seizures did occur after several weeks at fixed dose.
15 WELLBUTRIN should be discontinued and not restarted in patients who experience a
16 seizure while on treatment.

17 The risk of seizure is also related to patient factors, clinical situations, and concomitant
18 medications, which must be considered in selection of patients for therapy with
19 WELLBUTRIN.

- 20 • **Patient factors:** Predisposing factors that may increase the risk of seizure with
21 bupropion use include history of head trauma or prior seizure, CNS tumor, the
22 presence of severe hepatic cirrhosis, and concomitant medications that lower seizure
23 threshold.
- 24 • **Clinical situations:** Circumstances associated with an increased seizure risk include,
25 among others, excessive use of alcohol or sedatives (including benzodiazepines);
26 addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and
27 anorectics; and diabetes treated with oral hypoglycemics or insulin.
- 28 • **Concomitant medications:** Many medications (e.g., antipsychotics, antidepressants,
29 theophylline, systemic steroids) are known to lower seizure threshold.

30 ***Recommendations for Reducing the Risk of Seizure:*** Retrospective analysis of
31 clinical experience gained during the development of WELLBUTRIN suggests that the risk
32 of seizure may be minimized if

- 33 • the total daily dose of WELLBUTRIN does *not* exceed 450 mg,
- 34 • the daily dose is administered 3 times daily, with each single dose *not* to exceed 150 mg to
35 avoid high peak concentrations of bupropion and/or its metabolites, and
- 36 • the rate of incrementation of dose is very gradual.

37 Extreme caution should be used when WELLBUTRIN is administered to patients with a
38 history of seizure, cranial trauma, or other predisposition(s) toward seizure, or prescribed
39 with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic
40 steroids, etc.) that lower seizure threshold.

1 **Hepatic Impairment:** WELLBUTRIN should be used with extreme caution in patients
2 with severe hepatic cirrhosis. In these patients a reduced dose and/or frequency is required,
3 as peak bupropion, as well as AUC, levels are substantially increased and accumulation is
4 likely to occur in such patients to a greater extent than usual. The dose should not exceed
5 75 mg once a day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS,
6 and DOSAGE AND ADMINISTRATION).

7 **Potential for Hepatotoxicity:** In rats receiving large doses of bupropion chronically, there
8 was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In
9 dogs receiving large doses of bupropion chronically, various histologic changes were seen in the
10 liver, and laboratory tests suggesting mild hepatocellular injury were noted.

11 **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder, both adult
12 and pediatric, may experience worsening of their depression and/or the emergence of suicidal
13 ideation and behavior (suicidality), whether or not they are taking antidepressant medications,
14 and this risk may persist until significant remission occurs. Although there has been a long-
15 standing concern that antidepressants may have a role in inducing worsening of depression and
16 the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such
17 behaviors has not been established. **Nevertheless, patients being treated with antidepressants
18 should be observed closely for clinical worsening and suicidality, especially at the beginning
19 of a course of drug therapy, or at the time of dose changes, either increases or decreases.**

20 Consideration should be given to changing the therapeutic regimen, including possibly
21 discontinuing the medication in patients whose depression is persistently worse or whose
22 emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting
23 symptoms.

24 Because of the possibility of co-morbidity between major depressive disorder and other
25 psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients
26 with major depressive disorder should be observed when treating patients with other psychiatric
27 and nonpsychiatric disorders.

28 The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility
29 (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have
30 been reported in adult and pediatric patients being treated with antidepressants for major
31 depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.
32 Although a causal link between the emergence of such symptoms and either the worsening of
33 depression and/or the emergence of suicidal impulses has not been established, consideration
34 should be given to changing the therapeutic regimen, including possibly discontinuing the
35 medication in patients for whom such symptoms are severe, abrupt in onset, or were not part of
36 the patient's presenting symptoms.

37 **Families and caregivers of patients being treated with antidepressants for major
38 depressive disorder or other indications, both psychiatric and nonpsychiatric, should be
39 alerted about the need to monitor patients for the emergence of agitation, irritability, and
40 the other symptoms described above, as well as the emergence of suicidality, and to report**

1 **such symptoms immediately to health care providers.** Prescriptions for WELLBUTRIN
2 should be written for the smallest quantity of tablets consistent with good patient management, in
3 order to reduce the risk of overdose.

4 It should be noted that WELLBUTRIN is not approved for use in treating any indications in
5 the pediatric population.

6 A major depressive episode may be the initial presentation of bipolar disorder. It is generally
7 believed (although not established in controlled trials) that treating such an episode with an
8 antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in
9 patients at risk for bipolar disorder. Whether any of the symptoms described above represent
10 such a conversion is unknown. However, prior to initiating treatment with an antidepressant,
11 patients should be adequately screened to determine if they are at risk for bipolar disorder; such
12 screening should include a detailed psychiatric history, including a family history of suicide,
13 bipolar disorder, and depression. It should be noted that WELLBUTRIN is not approved for use
14 in treating bipolar depression.

15 **PRECAUTIONS**

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

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

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

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

38 **Allergic Reactions:** Anaphylactoid/anaphylactic reactions characterized by symptoms such
39 as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported

1 in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing
2 reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated
3 with bupropion. A patient should stop taking WELLBUTRIN and consult a doctor if
4 experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives,
5 chest pain, edema, and shortness of breath) during treatment.

6 Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed
7 hypersensitivity have been reported in association with bupropion. These symptoms may
8 resemble serum sickness.

9 **Cardiovascular Effects:** In clinical practice, hypertension, in some cases severe, requiring
10 acute treatment, has been reported in patients receiving bupropion alone and in combination with
11 nicotine replacement therapy. These events have been observed in both patients with and without
12 evidence of preexisting hypertension.

13 Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN[®]
14 Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-
15 release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher
16 incidence of treatment-emergent hypertension in patients treated with the combination of
17 sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the
18 combination of sustained-release bupropion and NTS had treatment-emergent hypertension
19 compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS,
20 and placebo, respectively. The majority of these patients had evidence of preexisting
21 hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and one
22 patient (0.4%) treated with NTS had study medication discontinued due to hypertension
23 compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure
24 is recommended in patients who receive the combination of bupropion and nicotine replacement.

25 There is no clinical experience establishing the safety of WELLBUTRIN in patients with a
26 recent history of myocardial infarction or unstable heart disease. Therefore, care should be
27 exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who
28 had previously developed orthostatic hypotension while receiving tricyclic antidepressants and
29 was also generally well tolerated in a group of 36 depressed inpatients with stable congestive
30 heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in
31 the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for
32 exacerbation of baseline hypertension.

33 **Hepatic Impairment:** WELLBUTRIN should be used with extreme caution in patients with
34 severe hepatic cirrhosis. In these patients, a reduced dose and frequency is required.
35 WELLBUTRIN should be used with caution in patients with hepatic impairment (including mild
36 to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in
37 patients with mild to moderate hepatic cirrhosis.

38 All patients with hepatic impairment should be closely monitored for possible adverse effects
39 that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY,
40 WARNINGS, and DOSAGE AND ADMINISTRATION).

1 **Renal Impairment:** No studies have been conducted in patients with renal impairment.
2 Bupropion is extensively metabolized in the liver to active metabolites, which are further
3 metabolized and subsequently excreted by the kidneys. WELLBUTRIN should be used with
4 caution in patients with renal impairment and a reduced frequency and/or dose should be
5 considered as bupropion and its metabolites may accumulate in such patients to a greater extent
6 than usual. The patient should be closely monitored for possible adverse effects that could
7 indicate high drug or metabolite levels.

8 **Information for Patients:** See the tear-off leaflet at the end of this labeling for Patient
9 Information.

10 Patients should be made aware that WELLBUTRIN contains the same active ingredient found
11 in ZYBAN, used as an aid to smoking cessation, and that WELLBUTRIN should not be used in
12 combination with ZYBAN or any other medications that contain bupropion hydrochloride.

13 Physicians are advised to discuss the following issues with patients:

14 Patients should be instructed to take WELLBUTRIN in equally divided doses 3 or 4 times a
15 day to minimize the risk of seizure.

16 Patients should be told that WELLBUTRIN should be discontinued and not restarted if they
17 experience a seizure while on treatment.

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

22 Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives
23 (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower
24 alcohol tolerance during treatment with WELLBUTRIN. Patients should be advised that the
25 consumption of alcohol should be minimized or avoided.

26 Patients and their families should be encouraged to be alert to the emergence of anxiety,
27 agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania,
28 worsening of depression, and suicidal ideation, especially early during antidepressant treatment.
29 Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt
30 in onset, or were not part of the patient's presenting symptoms.

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

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

36 **Laboratory Tests:** There are no specific laboratory tests recommended.

37 **Drug Interactions:** Few systemic data have been collected on the metabolism of
38 WELLBUTRIN following concomitant administration with other drugs or, alternatively, the
39 effect of concomitant administration of WELLBUTRIN on the metabolism of other drugs.

40 Because bupropion is extensively metabolized, the coadministration of other drugs may affect
41 its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to

1 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug
2 interaction between WELLBUTRIN and drugs that affect the CYP2B6 isoenzyme (e.g.,
3 orphenadrine and cyclophosphamide). The threohydrobupropion metabolite of bupropion does
4 not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant
5 administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites
6 were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg
7 sustained-release tablets with and without 800 mg of cimetidine, the pharmacokinetics of
8 bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases
9 in the AUC and C_{max} , respectively, of the combined moieties of threohydrobupropion and
10 erythrohydrobupropion.

11 While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g.,
12 carbamazepine, phenobarbital, phenytoin).

13 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in
14 humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to 8
15 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.
16 Nevertheless, there may be the potential for clinically important alterations of blood levels of
17 coadministered drugs.

18 **Drugs Metabolized by Cytochrome P450IID6 (CYP2D6):** Many drugs, including most
19 antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are
20 metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this
21 isoenzyme, bupropion and hydroxybupropion are inhibitors of the CYP2D6 isoenzyme in vitro.
22 In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the
23 CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single
24 dose of 50 mg desipramine increased the C_{max} , AUC, and $t_{1/2}$ of desipramine by an average of
25 approximately 2-, 5- and 2-fold, respectively. The effect was present for at least 7 days after the
26 last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6
27 has not been formally studied.

28 Therefore, co-administration of bupropion with drugs that are metabolized by CYP2D6
29 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine,
30 paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine),
31 beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide),
32 should be approached with caution and should be initiated at the lower end of the dose range of
33 the concomitant medication. If bupropion is added to the treatment regimen of a patient already
34 receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original
35 medication should be considered, particularly for those concomitant medications with a narrow
36 therapeutic index.

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

39 **Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of adverse
40 experiences in patients receiving bupropion concurrently with either levodopa or amantadine.
41 Administration of WELLBUTRIN Tablets to patients receiving either levodopa or amantadine
42 concurrently should be undertaken with caution, using small initial doses and small gradual dose
43 increases.

1 **Drugs that Lower Seizure Threshold:** Concurrent administration of WELLBUTRIN and
2 agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that
3 lower seizure threshold should be undertaken only with extreme caution (see WARNINGS).
4 Low initial dosing and small gradual dose increases should be employed.

5 **Nicotine Transdermal System:** (see PRECAUTIONS: Cardiovascular Effects).

6 **Alcohol:** In post-marketing experience, there have been rare reports of adverse
7 neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol
8 during treatment with WELLBUTRIN. The consumption of alcohol during treatment with
9 WELLBUTRIN should be minimized or avoided (also see CONTRAINDICATIONS).

10 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies
11 were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat
12 study there was an increase in nodular proliferative lesions of the liver at doses of 100 to
13 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be
14 precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen
15 in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in
16 either study.

17 Bupropion produced a borderline positive response (2 to 3 times control mutation rate) in
18 some strains in the Ames bacterial mutagenicity test, and a high oral dose (300 mg/kg, but not
19 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance
20 of these results in estimating the risk of human exposure to therapeutic doses is unknown.

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

23 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been
24 performed in rabbits and rats at doses up to 15 to 45 times the human daily dose and have
25 revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In
26 rabbits, a slightly increased incidence of fetal abnormalities was seen in 2 studies, but there was
27 no increase in any specific abnormality). There are no adequate and well-controlled studies in
28 pregnant women. Because animal reproduction studies are not always predictive of human
29 response, this drug should be used during pregnancy only if clearly needed.

30 To monitor fetal outcomes of pregnant women exposed to WELLBUTRIN, GlaxoSmithKline
31 maintains a Bupropion Pregnancy Registry. Health care providers are encouraged to register
32 patients by calling (800) 336-2176.

33 **Labor and Delivery:** The effect of WELLBUTRIN on labor and delivery in humans is
34 unknown.

35 **Nursing Mothers:** Like many other drugs, bupropion and its metabolites are secreted in human
36 milk. Because of the potential for serious adverse reactions in nursing infants from
37 WELLBUTRIN, a decision should be made whether to discontinue nursing or to discontinue the
38 drug, taking into account the importance of the drug to the mother.

39 **Pediatric Use:** The safety and effectiveness of WELLBUTRIN in pediatric patients under
40 18 years old have not been established. The immediate-release formulation of bupropion was

1 studied in 104 pediatric patients (age range, 6 to 16) in clinical trials of the drug for other
2 indications. Although generally well tolerated, the limited exposure is insufficient to assess the
3 safety of bupropion in pediatric patients (**see WARNINGS—Clinical Worsening and Suicide**
4 **Risk**).

5 **Geriatric Use:** Of the approximately 6,000 patients who participated in clinical trials with
6 bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and
7 over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in
8 clinical trials using the immediate-release formulation of bupropion (depression studies). No
9 overall differences in safety or effectiveness were observed between these subjects and younger
10 subjects, and other reported clinical experience has not identified differences in responses
11 between the elderly and younger patients, but greater sensitivity of some older individuals cannot
12 be ruled out.

13 A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its
14 metabolites in elderly subjects was similar to that of younger subjects; however, another
15 pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased
16 risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).

17 Bupropion is extensively metabolized in the liver to active metabolites, which are further
18 metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in
19 patients with impaired renal function. Because elderly patients are more likely to have decreased
20 renal function, care should be taken in dose selection, and it may be useful to monitor renal
21 function (see PRECAUTIONS: Renal Impairment and DOSAGE AND ADMINISTRATION).

22 **ADVERSE REACTIONS** (see also WARNINGS and PRECAUTIONS)

23 Adverse events commonly encountered in patients treated with WELLBUTRIN are agitation,
24 dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

25 Adverse events were sufficiently troublesome to cause discontinuation of treatment with
26 WELLBUTRIN in approximately 10% of the 2400 patients and volunteers who participated in
27 clinical trials during the product's initial development. The more common events causing
28 discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and
29 abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and
30 vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep
31 disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note,
32 however, that many of these events occurred at doses that exceed the recommended daily dose.

33 Accurate estimates of the incidence of adverse events associated with the use of any drug are
34 difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician
35 judgments, etc. Consequently, the table below is presented solely to indicate the relative
36 frequency of adverse events reported in representative controlled clinical studies conducted to
37 evaluate the safety and efficacy of WELLBUTRIN under relatively similar conditions of daily
38 dosage (300 to 600 mg), setting, and duration (3 to 4 weeks). The figures cited cannot be used to
39 predict precisely the incidence of untoward events in the course of usual medical practice where

1 patient characteristics and other factors must differ from those which prevailed in the clinical
 2 trials. These incidence figures also cannot be compared with those obtained from other clinical
 3 studies involving related drug products as each group of drug trials is conducted under a different
 4 set of conditions.

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

8
 9 **Table 1. Treatment Emergent Adverse Experience Incidence in Placebo-Controlled**
 10 **Clinical Trials* (Percent of Patients Reporting)**

Adverse Experience	WELLBUTRIN 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 disturbance	5.3	3.2
Blurred vision	14.6	10.3
Gustatory disturbance	3.1	1.1

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

2

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

1 The following definitions of frequency are used: Frequent adverse events are defined as those
2 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to
3 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

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

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

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

10 **Gastrointestinal:** Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice;
11 rare were rectal complaints, colitis, gastrointestinal bleeding, intestinal perforation, and stomach
12 ulcer.

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

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

18 **Musculoskeletal:** Rare was musculoskeletal chest pain.

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

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

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

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

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

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

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

37 **Body (General):** arthralgia, myalgia, and fever with rash and other symptoms suggestive of
38 delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

39 **Cardiovascular:** hypertension (in some cases severe, see PRECAUTIONS), orthostatic
40 hypotension, third degree heart block

1 **Endocrine:** syndrome of inappropriate antidiuretic hormone secretion, hyperglycemia,
2 hypoglycemia

3 **Gastrointestinal:** esophagitis, hepatitis, liver damage

4 **Hemic and Lymphatic:** ecchymosis, leukocytosis, leukopenia, thrombocytopenia. Altered
5 PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were
6 observed when bupropion was coadministered with warfarin.

7 **Musculoskeletal:** arthralgia, myalgia, muscle rigidity/fever/rhabdomyolysis, muscle
8 weakness

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

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

12 **Special Senses:** tinnitus

13 **DRUG ABUSE AND DEPENDENCE**

14 **Humans:** Controlled clinical studies conducted in normal volunteers, in subjects with a history
15 of multiple drug abuse, and in depressed patients showed some increase in motor activity and
16 agitation/excitement.

17 In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of
18 WELLBUTRIN produced mild amphetamine-like activity as compared to placebo on the
19 Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI) and a
20 score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These
21 scales measure general feelings of euphoria and drug desirability.

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

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

34 **OVERDOSAGE**

35 **Human Overdose Experience:** There has been extensive clinical experience with
36 overdosage of WELLBUTRIN Tablets. Thirteen overdoses occurred during clinical trials.
37 Twelve patients ingested 850 to 4,200 mg and recovered without significant sequelae. Another
38 patient who ingested 9,000 mg of WELLBUTRIN and 300 mg of tranlycypromine experienced a
39 grand mal seizure and recovered without further sequelae.

1 Since introduction, overdoses of WELLBUTRIN Tablets up to 17,500 mg have been reported.
2 Seizure was reported in approximately one third of all cases. Other serious reactions reported
3 with overdoses of WELLBUTRIN Tablets alone included hallucinations, loss of consciousness,
4 and sinus tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and
5 respiratory failure have been reported when WELLBUTRIN Tablets was part of multiple drug
6 overdoses.

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

11 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.
12 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first
13 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.
14 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with
15 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in
16 symptomatic patients.

17 Activated charcoal should be administered. There is no experience with the use of forced
18 diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion
19 overdoses. No specific antidotes for bupropion are known.

20 Due to the dose-related risk of seizures with WELLBUTRIN, hospitalization following
21 suspected overdose should be considered. Based on studies in animals, it is recommended that
22 seizures be treated with intravenous benzodiazepine administration and other supportive
23 measures, as appropriate.

24 In managing overdosage, consider the possibility of multiple drug involvement. The physician
25 should consider contacting a poison control center for additional information on the treatment of
26 any overdose. Telephone numbers for certified poison control centers are listed in the
27 *Physicians' Desk Reference* (PDR).

28 **DOSAGE AND ADMINISTRATION**

29 **General Dosing Considerations:** It is particularly important to administer WELLBUTRIN
30 in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose
31 should not exceed 100 mg/day in a 3-day period. Gradual escalation in dosage is also important
32 if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are
33 to be minimized. If necessary, these effects may be managed by temporary reduction of dose or
34 the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative
35 hypnotic usually is not required beyond the first week of treatment. Insomnia may also be
36 minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation
37 should be stopped.

38 No single dose of WELLBUTRIN should exceed 150 mg. WELLBUTRIN should be
39 administered 3 times daily, preferably with at least 6 hours between successive doses.

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

Table 2. Dosing Regimen

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

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of WELLBUTRIN may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75- or 100-mg tablets. The 100-mg tablet must be administered 4 times daily with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. WELLBUTRIN should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

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

Dosage Adjustment for Patients with Impaired Hepatic Function: WELLBUTRIN should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 75 mg once a day in these patients. WELLBUTRIN should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Dosage Adjustment for Patients with Impaired Renal Function: WELLBUTRIN should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED

WELLBUTRIN Tablets, 75 mg of bupropion hydrochloride, are yellow-gold, round, biconvex tablets printed with “WELLBUTRIN 75” in bottles of 100 (NDC 0173-0177-55).

WELLBUTRIN Tablets, 100 mg of bupropion hydrochloride, are red, round, biconvex tablets printed with “WELLBUTRIN 100” in bottles of 100 (NDC 0173-0178-55).

Store at 15° to 25°C (59° to 77°F). Protect from light and moisture.

