

PRODUCT MONOGRAPH

Pr ZYBAN®

Bupropion Hydrochloride

150 mg Sustained Release Tablets

Manufacturer's Standard

Smoking Cessation Aid

Valeant Canada LP
2150 St. Elzéar Blvd. West
Laval, QC,
H7L 4A8

Date of Revision:
July 22nd, 2020

Submission Control No: 237455

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Pr **ZYBAN**[®]

**Bupropion Hydrochloride
Sustained-release Tablets
Manufacturer's Standard**

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet / 150 mg	Carnauba wax, cysteine hydrochloride, FD&C Blue No. 2 Lake, FD&C Red No. 40 Lake, hydroxypropyl-methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, titanium dioxide. Tablets are printed with edible black ink

INDICATIONS AND CLINICAL USE

ZYBAN (bupropion hydrochloride) is indicated as smoking cessation treatment in conjunction with behavioural modification; nicotine replacement therapy may be used together with ZYBAN. Prior to a decision to prescribe a non-nicotine treatment including ZYBAN, thorough consideration should be given to the treatment option of nicotine replacement therapy alone.

Geriatrics (> 65 years of age):

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but because elderly patients are more likely to have decreased renal function, greater sensitivity of some older individuals to bupropion cannot be ruled out. (see **WARNINGS AND PRECAUTIONS, Renal Impairment**, and **DOSAGE AND ADMINISTRATION**)

Pediatrics (< 18 years of age):

The safety and efficacy of bupropion in pediatric patients have not been established. Therefore its use in this patient population is not recommended (see **WARNINGS AND PRECAUTIONS, Potential Association With the Occurrence of Behavioural and Emotional Changes, Including Self-Harm**).

CONTRAINDICATIONS

ZYBAN (bupropion hydrochloride) is contraindicated in patients who have shown an allergic response to bupropion or any other component of the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

To reduce the risk of seizures, ZYBAN (bupropion hydrochloride) is contraindicated in patients:

- **Receiving WELLBUTRIN XL, WELLBUTRIN SR or any other medications that contain bupropion hydrochloride because the incidence of seizure is dose dependent (see WARNINGS AND PRECAUTIONS)**
- With a current seizure disorder or history of seizures (see **WARNINGS AND PRECAUTIONS**)
- With a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures (see **WARNINGS AND PRECAUTIONS**) noted in patients treated for bulimia with the immediate release formulation of bupropion
- Undergoing abrupt withdrawal from alcohol or benzodiazepines or other sedatives

To reduce risks due to drug interaction, the concomitant use of ZYBAN is contraindicated in patients currently taking:

- Monoamine oxidase (MAO) inhibitors.
- The antipsychotic thioridazine, since bupropion may inhibit thioridazine metabolism, thus causing an increase in thioridazine levels and a potential increased risk of thioridazine-related serious ventricular arrhythmias and sudden death.

At least 14 days should elapse between discontinuation of one drug and the start of another.

WARNINGS AND PRECAUTIONS

POTENTIAL ASSOCIATION WITH THE OCCURRENCE OF BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

Although ZYBAN (bupropion hydrochloride) is not indicated for treatment of depression, it contains the same active ingredient - bupropion - as WELLBUTRIN SR and WELLBUTRIN XL anti-depressant medications. Therefore, clinicians should be aware of the following information.

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggests that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**
- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

Adults and Pediatrics: Additional Data

There are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, including bupropion, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression,

depersonalization. In some cases, the events occurred within several weeks of starting treatment.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

These neuropsychiatric symptoms have been reported in patients undergoing a smoking cessation attempt with ZYBAN, both with and without pre-existing psychiatric disorder. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking ZYBAN who continued to smoke. All patients being treated with ZYBAN should be observed for neuropsychiatric symptoms.

Seizures:

Patients should be made aware that ZYBAN (bupropion hydrochloride) Tablets contain the same active ingredient found in WELLBUTRIN SR Sustained Release Tablets and WELLBUTRIN XL Extended Release Tablets, used to treat depression, and that ZYBAN should NOT be administered to patients already receiving a product containing bupropion hydrochloride (see CONTRAINDICATIONS).

The use of bupropion is associated with a dose-dependent risk of seizures. *Clinicians should not prescribe doses over 300 mg/day for smoking cessation.* The risk of seizure is also related to patient factors, clinical situation, and concurrent medications, which must be considered in selection of patients for therapy with ZYBAN Tablets.

Seizures were not reported by patients participating in smoking cessation trials (n=1946). The seizure rate associated with doses of sustained-release bupropion up to 300 mg/day is approximately 0.1%. This incidence was prospectively determined during an 8-week treatment exposure in approximately 3,100 depressed patients. Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% in depressed patients treated at doses in a range of 300 to 450 mg/day. In addition, the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day.

Predisposing Risk Factors For Seizures:

The risk of seizure occurring with bupropion use appears to be associated with the presence of predisposing risk factors. Therefore, ZYBAN is contraindicated in patients with specific conditions (see **CONTRAINDICATIONS**), while extreme caution is recommended with other conditions, including:

- Prior seizure (see **CONTRAINDICATIONS**)
- History of head trauma
- Central nervous system (CNS) tumour
- The presence of severe hepatic impairment
- Excessive use of alcohol; addiction to opiates, cocaine, or stimulants

- Use of concomitant medications that lower seizure threshold, including but not limited to: antipsychotics, antidepressants, lithium, amantadine, theophylline, systemic steroids, quinolone antibiotics, and anti-malarials.
- Use of over-the-counter stimulants or anorectics
- Diabetes treated with oral hypoglycemics or insulin.

The above group of risk factors, including medications, should not be considered exhaustive; for each patient, all potential predisposing factors must be carefully considered.

In order to minimize the Risk of Seizure:

- **The total daily dose of ZYBAN must not exceed 300 mg (the maximum recommended dose), and**
- **No single dose of ZYBAN may exceed 150 mg, in order to avoid high peak concentrations of bupropion and/or its metabolites.**

If a Seizure Occurs:

Patients should be warned that if they experience a seizure while taking ZYBAN, they should contact their doctor or be taken to a hospital emergency ward immediately, and should stop taking ZYBAN. Treatment should not be restarted if a patient has experienced a seizure while taking ZYBAN, WELLBUTRIN SR, or WELLBUTRIN XL.

Serious Hypersensitivity Reactions

Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea have been reported at a rate of one to three per thousand in clinical trials. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking ZYBAN and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritis, hives, chest pain, edema, and shortness of breath) during treatment.

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

Bupropion should be discontinued immediately if any hypersensitivity reactions are experienced. Symptoms of hypersensitivity should be treated in accordance with established medical practice. Clinicians should be aware that symptoms may persist beyond the discontinuation of bupropion, and clinical management should be provided accordingly. In post-market experience, there have been reports of hypersensitivity reactions in patients who consumed alcohol while taking bupropion. As the contribution of alcohol to these reactions has been established, patients should avoid alcohol when they are taking bupropion (see **DRUG INTERACTIONS, Alcohol Interactions**).

Misuse of ZYBAN by injection or inhalation

ZYBAN is intended for oral use only. The inhalation of crushed tablets or injection of dissolved bupropion has been reported, and may lead to a rapid release, faster absorption and a potential overdose. Seizures and/or cases of death have been reported when bupropion has been

administered intra-nasally or by parenteral injection.

Potential for reduced efficacy of Tamoxifen

The anti-tumor agent tamoxifen is a pro-drug requiring metabolic activation by the liver enzyme CYP2D6. Drugs that are inhibitors of CYP2D6, including bupropion, may interfere with the efficacy of tamoxifen by reducing plasma concentrations of the primary active metabolite endoxifen. Therefore, bupropion should not be used in combination with tamoxifen, and other treatment options should be considered. (see **DRUG INTERACTIONS**).

Angle-Closure Glaucoma

Although ZYBAN is not indicated for treatment of depression, it contains bupropion, the same active ingredient as WELLBUTRIN SR and WELLBUTRIN XL anti-depressant medications, that can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

The following additional precautions are listed alphabetically.

Cardiovascular

In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of pre-existing hypertension.

Data from a comparative study of ZYBAN, nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of ZYBAN and NTS. In this study, 6.1% of patients treated with the combination of ZYBAN and NTS had treatment-emergent hypertension compared to 2.5%, 1.6% and 3.1% of patients treated with ZYBAN, NTS, and placebo, respectively. The majority of these patients had evidence of pre-existing hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of ZYBAN 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 depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable heart failure. However, bupropion was associated with a rise in supine blood pressure in the study of patients with stable heart failure, resulting in discontinuation of treatment in two patients for exacerbation of baseline hypertension.

Endocrine and Metabolism

See WARNINGS AND PRECAUTIONS, Potential for reduced efficacy of Tamoxifen

Changes in Body Weight

Weight gain is a well-known side effect of smoking cessation and may either impede initiation of a quit attempt or precipitate relapse.

Treatment: In clinical trials where treatment was for 7 to 12 weeks, a trend for lower body weight gain in subjects treated with bupropion as compared to those treated with placebo was noted. This trend was not maintained. One year after bupropion discontinuation, a trend to lower body weight gain in patients previously treated with placebo was detected.

Maintenance: In the study of up to 1 year treatment duration, patients treated with ZYBAN demonstrated significantly less weight gain ($p \leq 0.05$) than those patients treated with placebo throughout the study (8 lb versus 13 lb, respectively, at Week 52).

Hyponatremia

Hyponatremia cases have been reported very rarely with bupropion (see ADVERSE REACTIONS). Caution should be exercised in patients at risk, such as elderly patients or patients concomitantly treated with medications known to cause hyponatremia.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

The clearance of bupropion is reduced in all subjects with Child-Pugh Grades C hepatic impairment, and in some subjects with milder forms of liver impairment. Given the risks associated with both peak bupropion levels and drug accumulation ZYBAN is not recommended for use in patients with severe hepatic impairment. However, should clinical judgement deem it necessary, it should be used only with extreme caution at a reduced dose, to a maximum dose of 150 mg every other day.

Patients with mild or moderate hepatic impairment should be initiated at the reduced dose of 100 mg/day of bupropion, based on the variability reported for individual pharmacokinetic (PK) values of patients with mild hepatic impairment.

All patients with hepatic impairment should be closely monitored for possible adverse effects (e.g., insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels.

See also **DOSAGE AND ADMINISTRATION**; and also **ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency**

Neurologic

Serotonin Toxicity / Serotonin Syndrome

Serotonin toxicity has been reported in association with overdose (see **OVERDOSAGE**).

Serotonin toxicity, also known as serotonin syndrome, is a rare but potentially life-threatening condition. Serotonin toxicity may occur during combined use of bupropion with serotonergic drugs, such as with selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs), but has also been reported with bupropion overdose.

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, (in the presence of at least one a serotonergic agent), one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature $>38^{\circ}\text{C}$ and ocular clonus or inducible clonus.

If concomitant treatment with ZYBAN and a serotonergic drug is clinically warranted, the lowest effective dose of the serotonergic drug should be used and careful observation of the patient is advised, particularly during treatment initiation and dose increases.

If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

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.

Psychiatric

Insomnia

In the dose response smoking cessation trial, 29% of patients treated with 150 mg/day of ZYBAN (bupropion hydrochloride) and 35% of patients treated with 300 mg/day of ZYBAN experienced insomnia, compared to 21% of placebo treated patients. Symptoms were sufficiently severe to require discontinuation of treatment in 0.6% of patients treated with ZYBAN and none of the patients treated with placebo.

In the comparative trial, 40% of the patients treated with 300 mg/day of ZYBAN, 28% of the patients treated with 21 mg/day of nicotine transdermal system (NTS), and 45% of the patients treated with the combination of ZYBAN and NTS experienced insomnia compared to 18% of placebo treated patients. Symptoms were sufficiently severe to require discontinuation of treatment in 0.8% of patients treated with ZYBAN and none of the patients in the other three treatment groups.

Insomnia may be minimized by avoiding bedtime doses and, if necessary, reduction in dose.

Agitation-type emotional and behavioural changes

Agitation-type changes are reported for ZYBAN, and monitoring for these indicators of potential suicidal behaviour is advised in patients of all ages given a newer anti-depressant drug, including bupropion (See **WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH THE OCCURRENCE OF BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Psychosis, Confusion, and Other Neuropsychiatric Phenomena

In clinical trials with ZYBAN conducted in nondepressed smokers, the incidence of

neuropsychiatric side effects was generally comparable to placebo. Depressed patients treated with bupropion in depression trials have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania

Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible individuals. The sustained release formulation of bupropion is expected to pose similar risks. There were no reports of activation of psychosis or mania in clinical trials with ZYBAN conducted in nondepressed smokers.

Potential for Impaired Thinking and Motor Skills

Any psychoactive drug may impair judgement, thinking or motor skills. Therefore subjects should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect their performance adversely.

Renal

Renal Impairment:

There is no clinical experience establishing the safety of ZYBAN in patients with renal impairment. Bupropion is extensively metabolized in the liver to active metabolites, which are largely further metabolized before being excreted by the kidneys. ZYBAN should be used with caution in patients with renal impairment and a reduced frequency of dosing should be considered as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects (e.g., insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels.

Sensitivity/Resistance

***See WARNINGS AND PRECAUTIONS, Serious Hypersensitivity Reactions
Special Populations***

Pregnant Women:

Teratogenic Effects

Teratology studies have been performed at doses up to 450 mg/kg in rats (approximately 14 times the MRHD on a mg/m² basis) and at doses up to 150 mg/kg in rabbits (approximately 10 times the MRHD on a mg/m² basis). There is no evidence of impaired fertility or harm to the fetus due to bupropion. 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. Pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before pharmacological approaches are used.

First Trimester Exposure

Data from pregnancy registries have documented congenital malformations including cardiovascular (eg, ventricular and atrial septal defects) with maternal exposure to bupropion in the first trimester. Bupropion should be initiated during pregnancy or in women who intend to become pregnant only if benefits outweigh the potential risk to the fetus.

Third Trimester

Post-marketing reports indicate that some neonates exposed to ZYBAN, SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. The frequency of symptoms may vary with each drug. These features are consistent with either a direct toxic effect of SSRIs and other newer anti-depressants, or, possibly, a drug discontinuation syndrome. When treating a pregnant woman with ZYBAN during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. (See **DOSAGE AND ADMINISTRATION**)

Labour and Delivery

The effect of ZYBAN on labour and delivery in humans is unknown.

Nursing Women:

Bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ZYBAN, 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.

Pediatrics (< 18 years of age):

Clinical trials with ZYBAN did not include individuals under the age of 18. Therefore, the safety and efficacy in a pediatric smoking population have not been established.

Geriatrics (> 65 years of age):

Bupropion is extensively metabolized in the liver to active metabolites, of which some are eliminated by the kidneys, while others are further metabolized before being excreted in urine. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **WARNINGS AND PRECAUTIONS, Renal Impairment, and DOSAGE AND ADMINISTRATION**).

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

Of the approximately 6000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and

47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patient Counselling Information

Prior to prescribing ZYBAN, physicians should:

- Discuss with the patient the expected benefits and risks of ZYBAN as well as those of all smoking-cessation options. Patients should be informed that in many cases, nicotine replacement therapy should be tried before ZYBAN is prescribed.
- Inform their patients that the active ingredient in ZYBAN is bupropion, a drug also used to treat depression.
- Inform their patients that there is a chance that approximately 1 out of every 1000 people taking bupropion, the active ingredient in ZYBAN, will have a seizure. For this reason, ZYBAN may not be right for them. If the decision is for the patient to try ZYBAN, there are precautions to be aware of to help reduce the chances of a seizure (as below)

Patients receiving ZYBAN should be given the following instructions by the physicians:

- Patients should be instructed to read the Consumer Information before they start taking ZYBAN.
- Patients should also be provided with educational materials and necessary counselling to support an attempt at quitting smoking, including a review of the overall smoking cessation plan with the physician.
- **Patients should be informed that nicotine replacement therapy can be used with ZYBAN.**
- Patients should be reminded that the active ingredient in ZYBAN is bupropion, a drug also used to treat depression. Treatment with these types of medications is most safe and effective when patient and doctor have good on-going communication about how the patient is feeling. Patients should be advised that in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm, or harm to others. Should this happen, patients should be advised to get medical help immediately. Close observation by a doctor is necessary in this situation.
- Patients should be informed that they should never take the antidepressant WELLBUTRIN XL, or WELLBUTRIN SR with ZYBAN, nor ever take more than the recommended dose of ZYBAN. If they miss a dose, they should wait and take their next tablet at the regular time; they should not take double the dose. Also, other medications can increase the chances of seizure, including drugs for depression and some antibiotics.
- Patients should be advised to discuss the use of alcohol with their doctor before taking ZYBAN
- If a patient has signs of an allergic reaction such as a skin rash, or difficulty in breathing, they should stop taking ZYBAN and immediately contact their doctor or health care professional.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The information included under **ADVERSE REACTIONS** is based primarily on data from the dose-response trial and the comparative trial that evaluated ZYBAN (bupropion hydrochloride) for smoking cessation. Information on additional adverse events associated with the sustained-release formulation of bupropion, is included in a separate section (see **Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Events Associated with Discontinuation of Treatment

Adverse events caused discontinuation of treatment in 8% of the 706 patients treated with ZYBAN and 5% of the 313 patients treated with placebo. The more common events leading to discontinuation of treatment with ZYBAN included nervous system disturbances (3.4%), primarily tremors, and skin disorders (2.4%), primarily rashes.

Incidence of Commonly Observed Adverse Events

The most commonly observed adverse events consistently associated with the use of ZYBAN were dry mouth and insomnia. The most commonly observed adverse events were defined as those that consistently occurred at a rate of five percentage points greater than that for placebo across clinical studies.

Dose Dependency of Adverse Events

The incidence of dry mouth and insomnia may be related to the dose of ZYBAN. The occurrence of these adverse events may be minimized by reducing the dose of ZYBAN. In addition, insomnia may be minimized by avoiding bedtime doses.

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With ZYBAN

Table 1 enumerates selected treatment emergent adverse events from the dose response trial that occurred at an incidence of 1% or more and were more common in patients treated with ZYBAN compared to those treated with placebo. Table 2 enumerates selected treatment emergent adverse events from the comparative trial that occurred at an incidence of 1% or more and were more common in patients treated with ZYBAN, NTS, or the combination of ZYBAN and NTS compared to those treated with placebo. Reported adverse events were classified using a COSTART based dictionary.

TABLE 1 - Treatment-Emergent Adverse Event

Incidence in the Dose-Response Trial*

BODY SYSTEM	ADVERSE	ZYBAN	PLACEBO
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	EXPERIENCE	100-300mg/day (n=461) %	(n=150)%
BODY (General)	Neck pain	2	<1
	Allergic reaction	1	0
CARDIOVASCULAR	Hot flashes	1	0
	Hypertension	1	<1
DIGESTIVE	Dry mouth	11	5
	Increased appetite	2	<1
	Anorexia	1	<1
MUSCULOSKELETAL	Arthralgia	4	3
	Myalgia	2	1
NERVOUS SYSTEM	Insomnia	31	21
	Dizziness	8	7
	Tremor	2	1
	Somnolence	2	1
	Thinking abnormality	1	0
RESPIRATORY	Bronchitis	2	0
SKIN	Pruritis	3	<1
	Rash	3	<1
	Dry Skin	2	0
	Urticaria	1	0
SPECIAL SENSES	Taste Perversion	2	<1

*selected adverse events with an incidence of at least 1% of patients treated with ZYBAN and more frequent than in the placebo group.

TABLE 2 - Treatment-Emergent Adverse Event Incidences (%) in the Comparative Trial*

Adverse Experience	ZYBAN 300mg/day (n=243) %	Nicotine Transdermal System (NTS) 21mg/day (n=243) %	ZYBAN and NTS (n=244) %	Placebo (n=159) %
Body				
Abdominal pain	3	4	1	1
Accidental injury	2	2	1	1
Chest pain	<1	1	3	1
Neck Pain	2	1	<1	0
Facial edema	<1	0	1	0
Cardiovascular				
Hypertension	1	<1	2	0
Palpitations	2	0	1	0
Digestive				
Nausea	9	7	11	4
Dry Mouth	10	4	9	4
Constipation	8	4	9	3
Diarrhea	4	4	3	1
Anorexia	3	1	5	1
Mouth ulcer	2	1	1	1
Thirst	<1	<1	2	0
Musculoskeletal				
Myalgia	4	3	5	3
Arthralgia	5	3	3	2
Nervous System				
Insomnia	40	28	45	18
Dream abnormality	5	18	13	3
Anxiety	8	6	9	6
Disturbed concentration	9	3	9	4
Dizziness	10	2	8	6
Nervousness	4	<1	2	2
Tremor	1	<1	2	0
Dysphoria	<1	1	2	1
Respiratory				
Rhinitis	12	11	9	8
Increased cough	3	5	<1	1
Pharyngitis	3	2	3	0
Sinusitis	2	2	2	1
Dyspnea	1	0	2	1
Epistaxis	2	1	1	0
Skin				
Application site reaction	11	17	15	7
Rash	4	3	3	2
Pruritus	3	1	5	1
Urticaria	2	0	2	0
Special Senses				
Taste perversion	3	1	3	2
Tinnitus	1	0	<1	0

* Selected adverse events with an incidence of at least 1% of patients treated with ZYBAN, NTS, or the combination of ZYBAN and NTS and more frequent than in the placebo group.

In the relapse prevention study of up to 1 year in duration, ZYBAN was well tolerated. Adverse events were quantitatively and qualitatively similar to those observed in the dose-response and comparative trials.

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion

Post-marketing reports suggest that the reintroduction of ZYBAN in patients who experienced a seizure is associated with a risk of seizure reoccurrence in some cases. Thus, patients should not restart ZYBAN therapy if they have had a seizure on either bupropion formulation (ZYBAN, WELLBUTRIN XL, or WELLBUTRIN SR). (See **WARNINGS AND PRECAUTIONS, Seizures**)

In addition to the events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with bupropion sustained release. The frequencies represent the proportion of patients who experienced a treatment emergent adverse event on at least one occasion in placebo controlled studies for depression (n=987) or smoking cessation (n=1,013), or patients who experienced an adverse event requiring discontinuation of treatment in an open label surveillance study with bupropion sustained release tablets (n=3,100). All treatment emergent adverse events are included except those listed in Tables 1 and 2, those events listed in other safety related sections of the monograph, those adverse events subsumed under COSTART terms that are either overly general or excessively specified so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than two patients.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained release bupropion are included. The extent to which these events may be associated with ZYBAN is unknown.

Body (General)

Frequent were asthenia, fever, and headache. Infrequent were back pain, chills, inguinal hernia, musculoskeletal chest pain, pain, and photosensitivity. Rare was malaise.

Cardiovascular

Infrequent were flushing, migraine, postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were cardiovascular disorder, complete AV block,

extrasystoles, hypotension, hypertension (in some cases severe, see **WARNINGS AND PRECAUTIONS, Cardiovascular**), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive

Frequent were dyspepsia, flatulence, and vomiting. Infrequent were abnormal liver function, bruxism, dysphagia, gastric reflux, gingivitis, glossitis, jaundice, and stomatitis. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, increased salivation, intestinal perforation, liver damage, pancreatitis, stomach ulcer, and stool abnormality.

Endocrine

Also observed were hyperglycemia, hypoglycemia and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic

Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia.

Metabolic and Nutritional

Infrequent were edema, increased weight, and peripheral edema. Very rare was hyponatremia. Also observed was glycosuria.

Musculoskeletal

Infrequent were leg cramps and twitching. Also observed were arthritis and muscle rigidity/fever/rhabdomyolysis, and muscle weakness.

Nervous System

Frequent were agitation, depression, and irritability. Infrequent were abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory, depersonalization, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, paresthesia, suicidal ideation and vertigo. Rare were amnesia, ataxia, derealization, hypomania and seizure. Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive dyskinesia.

Respiratory

Rare was bronchospasm. Also observed was pneumonia.

Skin/Hypersensitivity

Frequent was sweating. Infrequent was acne and dry skin. Rare was maculopapular rash. Also observed were alopecia, angioedema, erythema multiforme, exfoliative dermatitis, hirsutism, and Steven-Johnson syndrome. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness.

Special Senses

Frequent was amblyopia. Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, and mydriasis.

Urogenital

Frequent was urinary frequency. Infrequent were impotence, polyuria, and urinary urgency. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, prostate disorder, salpingitis, urinary incontinence, urinary retention, urinary tract disorder, and vaginitis.

ZYBAN (bupropion hydrochloride) is likely to have a low abuse potential.

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by Cytochrome P450 11B6 (CYP2B6) isoenzyme. Therefore the potential exists for a drug interaction between ZYBAN and drugs that affect the CYP2B6 isoenzyme metabolism (e.g., orphenadrine, cyclophosphamide, ifosfamide, ticlopidine, and clopidogrel). The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes.

Few systematic data have been collected on the metabolism of bupropion following concomitant administration with other drugs, or alternatively, the effect of concomitant administration of ZYBAN on the metabolism of other drugs.

Animal data indicate that bupropion may be an inducer of drug-metabolizing enzymes in humans. However, following chronic administration of bupropion, 100 mg t.i.d. to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.

Bupropion is extensively metabolized. The coadministration of other drugs may affect its clinical activity. Carbamazepine, phenobarbital, phenytoin, ritonavir, and efavirenz may induce the metabolism of bupropion.

Drugs Metabolized by Cytochrome P450 IID6 (CYP2D6)

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

Concomitant therapy with drugs predominately metabolized by this isoenzyme (such as certain

beta-blockers, antiarrhythmics, serotonin selective reuptake inhibitors, tricyclic antidepressants, antipsychotics) should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a medication metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

Tamoxifen

Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Co-administration of this drug with strong CYP2D6 inhibitors such as bupropion can lead to reduced plasma concentrations of a primary active metabolite (endoxifen). Therefore, since chronic use of CYP2D6 inhibitors together with tamoxifen can result in reduced efficacy of tamoxifen, bupropion should not be used in combination with tamoxifen and other treatment options should be considered (see **WARNINGS AND PRECAUTIONS**).

Citalopram

Although citalopram (a SSRI) is not primarily metabolized by CYP2D6, in one study (a 3-period, sequential-treatment, crossover study in 30 healthy volunteers), bupropion increased the C_{max} and AUC of citalopram by 30% and 40% respectively. Citalopram did not significantly alter the pharmacokinetics of bupropion in this study.

Ritonavir and Efavirenz

In an open-label, two-phase, sequential study of 64 healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir 400 mg (Kaletra[®]) twice daily reduced the exposure of bupropion (150-300 mg daily) and its major metabolites in a dose dependent manner by approximately 20 to 80%. Similarly, efavirenz 600 mg once daily for two weeks reduced the exposure of a single oral 150 mg dose of bupropion by approximately 55% in 13 healthy volunteers (18-55 years of age). This effect of ritonavir/Kaletra[®] and efavirenz is thought to be due to the induction of bupropion metabolism and can be clinically significant. Patients receiving any of these drugs with bupropion may need increased doses of bupropion but the maximum recommended daily dose of bupropion should not be exceeded. The effects of bupropion on the PK parameters of ritonavir/Kaletra[®] and efavirenz have not been studied.

Co-administration of Thioridazine Contraindicated

Administration of the antipsychotic thioridazine alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias such as torsades de pointes, and sudden death. As this effect appears to be dose-related, it is anticipated that risk increases with inhibition of thioridazine metabolism. An in-vivo study suggests that drugs which inhibit CYP2D6 will elevate plasma levels of thioridazine. Therefore concomitant use of thioridazine with ZYBAN is contraindicated (see **CONTRAINDICATIONS**).

Co-administration of other drugs metabolized by CYP2D6 isoenzyme

Co-administration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline, venlafaxine), antipsychotics (e.g., haloperidol, risperidone), beta-blockers (e.g., metoprolol, bisoprolol, carvedilol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the

dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

MAO Inhibitors

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. Concomitant use of bupropion and MAO inhibitors is contraindicated. At least 14 days should elapse between discontinuation of MAO inhibitors and initiation of treatment with bupropion (see **CONTRAINDICATIONS**).

Cimetidine:

The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were examined in a crossover study in 24 healthy young male volunteers, following oral administration of two 150 mg bupropion sustained release tablets with and without 800 mg of cimetidine. A single dose of cimetidine had no effect on single dose pharmacokinetic parameter estimates for bupropion, or hydroxybupropion, but caused a small statistically significant increase in the combined threohydro and erythro bupropion AUC (16%) and C_{max} (32%).

Lamotrigine:

In a randomized, cross-over study of 12 healthy volunteers, multiple 150 mg bid oral doses of bupropion sustained release formulation had no statistically significant effect on the single (100 mg) dose pharmacokinetics of lamotrigine and had only a 15% increase in the AUC of its metabolite (lamotrigine glucuronide), which is not considered clinically significant. The effect(s) of lamotrigine on pharmacokinetics of bupropion is unknown.

Levodopa and Amantadine

Limited clinical data suggest a higher incidence of neuropsychiatric adverse experiences, such as confusion, agitation and delirium, in patients receiving bupropion concurrently with either levodopa or amantadine. Tremor, ataxia and dizziness were also reported. Administration of ZYBAN to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

Clopidogrel and Ticlopidine:

Both clopidogrel and ticlopidine have been shown to significantly inhibit CYP2B6-catalysed bupropion hydroxylation. The mean area under the plasma concentration-time curve (AUC) of hydroxybupropion was reduced by 52% by clopidogrel and by 84% by ticlopidine. The AUC of bupropion was increased by 60% with clopidogrel and by 85% with ticlopidine. Therefore, concomitant administration of bupropion and either clopidogrel or ticlopidine may result in increased plasma concentrations of bupropion and reduced concentrations of hydroxybupropion. This may affect the efficacy of bupropion and may also increase the risk of concentration-dependent adverse events of bupropion, such as seizures (see **WARNINGS AND PRECAUTIONS, Seizures**). Patients receiving drugs used to reduce blood clots (such as either clopidogrel and/or ticlopidine) are likely to require dose adjustments of bupropion.

Digoxin:

Co-administration of digoxin with bupropion may decrease digoxin level. A clinical report suggests that when administered ~24 hours before digoxin, bupropion (extended release 150 mg) decreases digoxin AUC 0-24 h 1.6-fold and increases renal clearance 1.8 fold in healthy volunteers. Caution is advised when concomitant administration of ZYBAN and digoxin is required.

Use of ZYBAN with Drugs that Predispose Patients to Seizures

Concurrent administration of ZYBAN with agents (e.g., antipsychotics, antidepressants, theophylline, lithium, amantadine, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see **WARNINGS AND PRECAUTIONS**). Low initial dosing and gradual dose increases should be employed.

Use of ZYBAN with other Drugs with CNS activity:

The risks of bupropion in combination with other CNS-active drugs have not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZYBAN and such drugs is required.

Nicotine Transdermal System

See **WARNINGS AND PRECAUTIONS, Cardiovascular**.

Smoking Cessation

Physiological changes resulting from smoking cessation itself, with or without treatment with ZYBAN, may alter the pharmacokinetics of some concomitant medications, which may require dosage adjustment.

Alcohol Interactions:

In post-marketing experience, there have been reports of adverse neuropsychiatric events or, reduced alcohol tolerance, in patients who were drinking alcohol during treatment with bupropion. Rarely, reports of fatal outcomes with this combination have been received, however a causal relationship has not been established. The consumption of alcohol during treatment with bupropion should be avoided (also see **WARNINGS AND PRECAUTIONS, Predisposing Risk Factors for Seizures**).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

ZYBAN (bupropion hydrochloride) is not indicated for use in children under 18 years of age.

Prior to a decision to prescribe non-nicotine treatment including ZYBAN, thorough consideration should be given to the treatment option of nicotine replacement therapy alone.

Usual Dosage for Adults

The recommended and maximum dose of ZYBAN (bupropion hydrochloride) is 300 mg/day, given as 150 mg twice daily. Dosing should begin at 150 mg once daily for the first 3 days, followed by a dose increase to the recommended usual dose of 300 mg/day as necessary. There

should be an interval of at least 8 hours between successive doses. **In order to minimize the risk of seizures, single doses of ZYBAN must not exceed 150 mg and** doses above 300 mg/day must not be used (see **WARNINGS AND PRECAUTIONS**).

Treatment with ZYBAN should be initiated **while the patient is still smoking**, since approximately 1 week of treatment is required to achieve steady state blood levels of bupropion. Patients should set a "target quit date" within the first 2 weeks of treatment with ZYBAN, generally in the second week. Treatment with ZYBAN should be continued for 7 to 12 weeks; duration of treatment should be based on the relative benefits and risks for individual patients. If a patient has not made significant progress towards abstinence by the seventh week of therapy with ZYBAN, it is unlikely that he or she will quit during that attempt, and treatment should probably be discontinued. Dose tapering of ZYBAN is not required when discontinuing treatment. It is important that patients continue to receive counseling and support throughout treatment with ZYBAN, and for a period of time thereafter.

Maintenance: Nicotine dependence is a chronic condition. Many patients attempting to quit smoking experience multiple relapses. Systematic evaluation of ZYBAN 300 mg/day for the prevention of relapse demonstrated that treatment for up to 1 year was well tolerated and efficacious in preventing relapse (see **ACTION AND CLINICAL PHARMACOLOGY**). Whether to continue treatment with ZYBAN for periods longer than 12 weeks must be determined for individual patients.

Patients should be advised to swallow ZYBAN Tablets whole with fluids, and NOT to chew, divide, crush or otherwise tamper with the tablets in any way that might affect the release rate of bupropion.

Missed Dose

ZYBAN should be taken at the same time each day and no more than the recommended dose should be taken each day. If the normal administration time has been missed, the dose should be skipped and administration resumed at the normal administration time of the following day.

Treatment of Pregnant Women During the Third Trimester

Post-marketing reports indicate that some neonates exposed to ZYBAN, SSRIs, or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **WARNINGS AND PRECAUTIONS**). When treating pregnant women with ZYBAN during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering ZYBAN in the third trimester.

Administration

Geriatric Use

The elderly are at increased risk for accumulation of bupropion and its metabolites, including due to likelihood of decreased renal function. Therefore, care should be taken in dose selection, and it may be useful to monitor renal function. (See **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**)

Dosage Adjustment for Patients with Impaired Hepatic Function

Mild and Moderate Hepatic Impairment: Given the variable pharmacokinetics of bupropion in patients with either mild or moderate hepatic impairment (Child-Pugh Grade A or B), treatment should be initiated at 100 mg/day of bupropion. Maintenance dose may be adjusted according to clinical response and tolerance. Caution should be exercised as there is no clinical experience with ZYBAN in hepatically impaired patients (see also **WARNINGS AND PRECAUTIONS**).

Severe Impairment: Given the risks associated with both peak bupropion levels and drug accumulation. ZYBAN is not recommended for use in patients with severe hepatic impairment. However, should clinical judgement deem it necessary, the drug should be used only with extreme caution (see also **WARNINGS AND PRECAUTIONS**). The dose should not exceed 150 mg every other day in these patients. Any theoretical dose reduction for this patient population based on the findings of the pharmacokinetic studies may result in toxic drug levels in these patients (see **WARNINGS AND PRECAUTIONS, DETAILED PHARMACOLOGY Subgroup Analysis**).

Dosage Adjustment for Patients with Impaired Renal Function

ZYBAN should be used with caution in patients with renal impairment due to the potential for drug accumulation, and a reduced frequency of dosing should be considered (see **WARNINGS AND PRECAUTIONS, Renal Impairment** and **PHARMACOLOGY, Subgroup Analysis**).

All patients with hepatic or renal impairment should be closely monitored for possible adverse effects (e.g., insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels.

Individualization of Therapy

Patients are more likely to quit smoking and remain abstinent if they are seen frequently and receive support from their physicians or other health care professionals. It is important to ensure that patients read the instructions provided to them and have their questions answered. Physicians should review the patient's overall smoking cessation program that includes treatment with ZYBAN. Patients should be advised of the importance of participating in the behavioural interventions, counselling, and/or support services to be used in conjunction with ZYBAN.

The goal of therapy with ZYBAN is complete abstinence. If a patient has not made significant progress towards abstinence by the seventh week of therapy with ZYBAN, it is unlikely that he or she will quit during that attempt, and treatment should be discontinued.

Patients who fail to quit smoking during an attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who are unsuccessful should be evaluated to determine why they failed. A new quit attempt should be encouraged when factors that contributed to failure can be eliminated or reduced, and conditions are more favourable.

Combination Treatment With ZYBAN and a Nicotine Transdermal System (NTS)

ZYBAN may be prescribed in combination with NTS for smoking cessation. The prescriber should review the complete prescribing information for both ZYBAN and NTS before using combination treatment. Treatment with ZYBAN is initiated at 150mg/day while the patient is still smoking and increased after 3 days to 300mg/day given at 150 mg twice daily. Nicotine

transdermal system (NTS) may be added to treatment with ZYBAN after approximately 1 week when the patient has reached the target quit date. During weeks 8 and 9, NTS should be tapered (see **ACTIONS AND CLINICAL PHARMACOLOGY, CLINICAL TRIALS**). Monitoring for treatment emergent hypertension in patients treated with the combination of ZYBAN and NTS is recommended.

OVERDOSAGE

Human Overdose Experience

In addition to those events reported under *Adverse Reactions*, overdose has resulted in symptoms including drowsiness, loss of consciousness and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias.

There has been very limited experience with overdosage of the sustained-release formulation of bupropion; three such cases were reported during clinical trials in depressed patients. One patient ingested 3000 mg of bupropion sustained-release tablets and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a "handful" of bupropion sustained-release tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3600 mg of bupropion sustained-release tablets and a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess". None of the patients experienced further sequelae.

There has been extensive experience with overdoses of the immediate-release formulation of bupropion. Thirteen overdoses occurred during clinical trials in depressed patients. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of immediate-release bupropion and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

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

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

Serotonin toxicity has been reported with bupropion overdose during postmarketing experience (see WARNINGS AND PRECAUTIONS, Neurologic).

Management of Overdose

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In the event of overdose, hospitalisation is advised. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm (ECG) and vital signs. EEG monitoring is also recommended for the first 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

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

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

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Compendium of Pharmaceuticals and Specialties (CPS)*.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism by which ZYBAN[®] (bupropion hydrochloride) enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms. ZYBAN is a weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. ZYBAN is chemically unrelated to nicotine or other agents currently used in the treatment of nicotine addiction.

Bupropion, initially developed as an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitors or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines.

Pharmacokinetics

Following oral administration of ZYBAN Tablets to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. Food increased C_{max} and AUC of bupropion by 11% and 17%, respectively, indicating that there is no clinically significant food effect. In vitro tests indicate that bupropion is 84% bound to human albumin at plasma concentrations up to 200 µg/mL.

The mean elimination half-life (\pm SD) of bupropion after chronic dosing is 21 (\pm 9) hours, and steady-state plasma concentrations of bupropion are reached within 5 days (See **DETAILED PHARMACOLOGY, Human Pharmacokinetics**).

Three active metabolites have been identified. Bupropion and its metabolites exhibit linear kinetics following chronic administration of 150 to 300 mg/day. Plasma concentrations of the metabolites exceed those of the parent drug and may be clinically important (See **DETAILED PHARMACOLOGY, Human Pharmacokinetics**).

The Nicotine Transdermal System (NTS) used in clinical trials did not appear to have effects on the pharmacokinetics of ZYBAN. Smokers and non-smokers appear to have similar pharmacokinetics of bupropion or its major metabolites.

Special Populations and Conditions

Pediatrics: Clinical trials with ZYBAN did not include individuals under the age of 18. Therefore, the safety and efficacy in a pediatric smoking population have not been established.

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

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

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in two single-dose studies, one in subjects with alcoholic liver disease and one in subjects with mild to severe cirrhosis. The first study involved 8 subjects with alcoholic liver disease, and 8 healthy matched controls. While mean AUC values were not significantly different, individual AUC values for both the parent drug bupropion and the primary metabolite hydroxybupropion were more variable in subjects with alcoholic liver disease, and increased by approximately 50% over those of healthy volunteers. The mean half-life of the primary metabolite hydroxybupropion was significantly longer by approximately 40% in subjects with alcoholic liver disease than in healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). For all other pharmacokinetic values, for both parent drug and metabolites, there were minimal differences between the two groups.

The second study involved 17 subjects with hepatic impairment (n = 9 mild/Grade A Child-Pugh rating; n = 8 severe/Grade C Child-Pugh rating) and 8 healthy matched controls. In the severe

group, the mean value for bupropion AUC was increased threefold over control values, with mean clearance decreased proportionately. Mean C_{max} and plasma half-life were increased by approximately 70% and 40% respectively. For the primary metabolites, mean AUC was increased by approximately 30% - 50%, with mean clearance decreased proportionately. Mean C_{max} was lower by approximately 30% to 70%, and mean plasma half life increased threefold.

In the mild group, while mean values were not statistically increased from those of controls, the variability in the PK values was higher in the subjects with impairment; a sub-group of 1 to 3 subjects (dependent on pharmacokinetic parameter examined) showed individual values which were in the range of the severely impaired subjects. For the primary metabolites, the differences between groups in pharmacokinetic parameters were minimal. The levels of unbound drug were not assessed for any group.

In patients with hepatic impairment, treatment should be initiated at reduced dosage (see **WARNINGS AND PRECAUTIONS**, see **DOSAGE AND ADMINISTRATION**).

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

STORAGE AND STABILITY

Store at 15°C to 25°C. Store in a dry place, protected from light.

SPECIAL HANDLING INSTRUCTIONS

None

DOSAGE FORMS, COMPOSITION AND PACKAGING

ZYBAN (bupropion hydrochloride) is supplied as a kit containing 100 blistered tablets in the following strength: 150 mg (purple) round, biconvex film-coated tablets printed "ZYBAN 150".

ZYBAN (bupropion hydrochloride) Tablets contain 150 mg of bupropion hydrochloride. The tablets also contain the following non-medicinal ingredients: carnauba wax, cysteine hydrochloride, FD&C Blue No. 2 Lake, FD&C Red No. 40 Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, titanium dioxide and are printed with edible black ink.

PART II: SCIENTIFIC INFORMATION

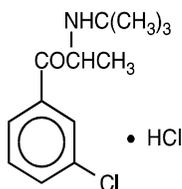
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Bupropion hydrochloride

Chemical Name: (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride

Structural Formula:



Molecular Formula: C₁₃H₁₈ClNO • HCl

Molecular Weight: 276.2 daltons

Description: Bupropion hydrochloride is a white powder with slight characteristic odour and has a maximum solubility in water of 312 mg/mL @ 25°C.

CLINICAL TRIALS

Study demographics and trial design

The efficacy of ZYBAN (bupropion hydrochloride) as an aid to smoking cessation was demonstrated in two placebo controlled, double blind trials in nondepressed chronic cigarette smokers (n=1,508, ≥15 cigarettes per day). In a third study, the efficacy of chronic administration (up to 1 year) of ZYBAN in preventing relapse to smoking was studied in a placebo-controlled, double-blind trial of nondepressed chronic cigarette smokers (n=432, ≥15 cigarettes per day). In these studies, ZYBAN was used in conjunction with individual smoking cessation counseling.

Study results

The first study was a dose response trial conducted at three clinical centres. Patients in this study were treated for 7 weeks with one of three doses of ZYBAN (100, 150, or 300 mg/day) or placebo; quitting was defined as total abstinence during the last 4 weeks of treatment (weeks 4 through 7). Abstinence was determined by patient daily diaries and verified by carbon monoxide levels in expired air.

Table 3 shows a dose dependent increase in the percentage of patients able to achieve 4 week abstinence (weeks 4 through 7). Treatment with ZYBAN at both 150 and 300 mg/day was significantly more effective than placebo, in this study. Treatment with ZYBAN (7 weeks at 300 mg/day) was more effective than placebo in helping patients maintain continuous abstinence through week 26 (6 months) of the study.

Table 3
Dose-Response Trial: Quit Rates by Treatment Group
(Intent to Treat Analysis)

Abstinence From Week 4 Through Specified Week	Treatment Groups			
	Placebo (n = 151) % (95% CI)	ZYBAN 100 mg/day (n = 153) % (95% CI)	ZYBAN 150 mg/day (n = 153) % (95% CI)	ZYBAN 300 mg/day (n = 156) % (95% CI)
Week 7 (4-week quit)	17% (11-23)	22% (15-28)	27%* (20-35)	36%* (28-43)
Week 12	14% (8-19)	20% (13-26)	20% (14-27)	25%* (18-32)
Week 26	11% (6-16)	16% (11-22)	18% (12-24)	19%* (13-25)

Quit rates are the proportions of all persons initially enrolled who abstained from week 4 of the study through the specified week.

* Significantly different from placebo ($P \leq 0.05$).

The second study was a comparative trial conducted at four clinical centers. Four treatments were evaluated: ZYBAN 300 mg/day, HABITROL^{®1} (nicotine transdermal system) (NTS) 21

¹ Registered Trademark of Novartis Consumer Health Canada Inc.

mg/day, combination of ZYBAN 300 mg/day plus NTS 21 mg/day, and placebo. Patients were treated with ZYBAN for 9 weeks. Treatment with ZYBAN was initiated at 150 mg/day while the patient was still smoking and was increased after 3 days to 300 mg/day given as 150 mg twice daily. NTS 21 mg/day was added to treatment with ZYBAN after approximately 1 week when the patient reached the target quit date. During weeks 8 and 9 of the study, NTS was tapered to 14 and 7 mg/day, respectively. Quitting, defined as total abstinence during weeks 4 through 7, was determined by patient daily diaries and verified by expired air carbon monoxide levels.

In this study (Table 4), patients treated with either ZYBAN or NTS achieved greater 4 week abstinence rates than patients treated with placebo. In addition, patients treated with the combination of ZYBAN and NTS achieved higher 4 week abstinence rates than patients treated with either of the individual active treatments alone, although only the comparison with NTS achieved statistical significance. Both ZYBAN and the combination of ZYBAN and NTS were more effective than placebo and NTS in helping patients maintain abstinence through week 52 of the study. Although the treatment combination of ZYBAN and NTS displayed the highest rates of continuous abstinence throughout the study, the quit rates for the combination were not significantly higher ($P > 0.05$) than for ZYBAN alone. Quit rates for ZYBAN were similar in patients with and without prior quit attempts using nicotine replacement therapy.

Table 4
Comparative Trial: Quit Rates by Treatment Group

Abstinence From Week 4 Through Specified Week	Treatment Groups			
	Placebo (n = 160) % (95% CI)	Nicotine Transdermal System (NTS) 21 mg/day (n = 244) % (95% CI)	ZYBAN 300 mg/day (n = 244) % (95% CI)	ZYBAN 300 mg/day and NTS 21 mg/day (n = 245) % (95% CI)
Week 7 (4-week quit)	23% (17-30)	36%* (30-42)	49%* ^I (43-56)	58%* ^I (51-64)
Week 12	20% (14-26)	29% ^H (23-34)	41%* ^I (34-47)	48%* ^I (42-54)
Week 26	13% (7-18)	18% (14-23)	30%* ^I (24-35)	33%* ^I (27-39)
Week 52	8% (3-12)	12% (8-16)	23%* ^I (18-28)	28%* ^I (23-34)

* $P < 0.01$ versus placebo.

^H $P < 0.05$ versus placebo.

^I $P < 0.01$ versus NTS.

The third study was a long-term relapse prevention trial conducted at five clinical centers. Patients in this study received open-label ZYBAN 300mg/day for 7 weeks. Patients who quit smoking while receiving ZYBAN were then randomized to ZYBAN 300 mg/day or placebo for a total study duration of 1 year. Abstinence from smoking was determined by patient self-report and verified by expired air carbon monoxide levels. Relapse was defined as the first cigarette

smoked.

Results of this 1-year trial demonstrated statistically significantly less relapse to smoking for those patients taking ZYBAN compared to those taking placebo. The time for 50% of the patients to relapse to smoking was significantly longer for ZYBAN compared to placebo (32 weeks versus 20 weeks). Continuous abstinence rates were greater for those patients randomized to ZYBAN as compared to placebo through 6 months ($P < 0.05$; 55% versus 44%). At 1 year, point prevalence abstinence rates only (abstinence from smoking for the 7 consecutive days preceding the clinic visit) were significantly higher for patients treated with ZYBAN compared to placebo-treated patients ($P < 0.01$; 55% versus 42%).

Treatment with ZYBAN reduced some of the withdrawal symptoms compared to placebo: irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; and depressed mood or negative affect. Depending on the study and the measure used, treatment with ZYBAN showed evidence of reduction in craving for cigarettes or urge to smoke compared to placebo.

DETAILED PHARMACOLOGY

Human Pharmacokinetics

Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied. Bupropion follows biphasic pharmacokinetics best described by a two compartment model. The terminal phase has a mean half life ($\pm\%$ CV) of about 21 hours ($\pm 20\%$), while the distribution phase has a mean half life of 3 to 4 hours.

Absorption

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 150 to 300 mg/day.

Bupropion has not been administered intravenously to humans; therefore, the absolute bioavailability of ZYBAN Sustained Release Tablets in humans has not been determined. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

Following oral administration of ZYBAN to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. The mean peak concentration (C_{max}) values were 91 and 143 ng/mL from two single dose (150 mg) studies. At steady state, the mean C_{max} following a 150 mg dose every 12 hours is 136 ng/mL.

Three studies in healthy volunteers suggest that exposure to bupropion may be increased when sustained release bupropion tablets are taken with food. When taken following food, peak plasma concentration of bupropion (C_{max}) increased by 11%, 16% and 35% in three studies. The overall exposure to bupropion (AUC) increased by 17%, 17% and 19% in these three studies.

Distribution

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to

that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion. The volume of distribution (V_{ss}/F) estimated from a single 150 mg dose given to 17 subjects is 1,950 L (20% CV).

Metabolism

Bupropion is extensively metabolized in humans. There are three active metabolites: hydroxybupropion and the amino alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via hydroxylation of the tert butyl group of bupropion and/or reduction of the carbonyl group. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized; however, it has been demonstrated in mice that hydroxybupropion is comparable in potency to bupropion, while the other metabolites are one tenth to one half as potent. This may be of clinical importance because the plasma concentrations of the metabolites are higher than those of bupropion. In vitro findings suggest that cytochrome P450 11B6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450 11B6 isoenzyme (see PRECAUTIONS, Drug Interactions). Although bupropion is not metabolized by cytochrome P450 11D6, there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see PRECAUTIONS, Drugs Metabolized by Cytochrome P450 11D6).

Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state. The AUC at steady state is about 17 times that of bupropion.

The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite, and steady state AUCs are 1.5 and 7 times that of bupropion, respectively.

The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150 mg dose of ZYBAN, there was no statistically significant difference in C_{max} , half-life, t_{max} , AUC, or clearance of bupropion or its major metabolites between smokers and nonsmokers.

Elimination

The mean (\pm % CV) apparent clearance (Cl/F) estimated from two single dose (150 mg) studies are 135 (\pm 20%) and 209 L/hr (\pm 21%). Following chronic dosing of 150 mg of ZYBAN every 12 hours for 14 days ($n=34$), the mean Cl/F at steady state was 160 L/hr (\pm 23%). The mean elimination half life of bupropion estimated from a series of studies is approximately 21 hours. Estimates of the half lives of the metabolites determined from a multiple dose study were 20 hours (\pm 25%) for hydroxybupropion, 37 hours (\pm 35%) for threohydrobupropion, and 33 hours

(±30%) for erythrohydrobupropion. Steady state plasma concentrations of bupropion and metabolites are reached within 5 and 8 days, respectively.

Following oral administration of 200 mg of ¹⁴C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%.

Human Pharmacokinetics: Subgroup Analysis

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 the active metabolites of bupropion. 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 further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic (See also WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION)

The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in two single-dose studies, one in subjects with alcoholic liver disease and one in subjects with mild to severe cirrhosis. The first study involved 8 subjects with alcoholic liver disease, and 8 healthy matched controls. While mean AUC values were not significantly different, individual AUC values for both the parent drug bupropion and the primary metabolite hydroxybupropion were more variable in subjects with alcoholic liver disease, and increased by approximately 50% over those of healthy volunteers. The mean half-life of the primary metabolite hydroxybupropion was significantly longer by approximately 40% in subjects with alcoholic liver disease than in healthy volunteers (32±14 hours versus 21±5 hours, respectively). For all other pharmacokinetic values, for both parent drug and metabolites, there were minimal differences between the two groups.

The second study involved 17 subjects with hepatic impairment (n = 9 mild/Grade A Child-Pugh rating; n = 8 severe/Grade C Child-Pugh rating) and 8 healthy matched controls. In the severe group, the mean value for bupropion AUC was increased threefold over control values, with mean clearance decreased proportionately. Mean C_{max} and plasma half-life were increased by approximately 70% and 40% respectively. For the primary metabolites, mean AUC was increased by approximately 30% - 50%, with mean clearance decreased proportionately. Mean C_{max} was lower by approximately 30% to 70%, and mean plasma half life increased threefold.

In the mild group, while mean values were not statistically increased from those of controls, the variability in the PK values was higher in the subjects with impairment; a sub-group of 1 to 3 subjects (dependent on pharmacokinetic parameter examined) showed individual values which were in the range of the severely impaired subjects. For the primary metabolites, the differences between groups in pharmacokinetic parameters were minimal. The levels of unbound drug were not assessed for any group.

In patients with hepatic impairment, treatment should be initiated at reduced dosage (see **WARNINGS AND PRECAUTIONS**, see **DOSAGE AND ADMINISTRATION**).

Renal

The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction

During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of congestive heart failure [CHF] or an enlarged heart on x ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared to healthy normal volunteers, was revealed.

Age

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

Gender

A single dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex related differences in the pharmacokinetic parameters of bupropion.

TOXICOLOGY

In a 14-day oral toxicity study in rats, a reversible dose-related increase in absolute and relative liver weights (approximately 5-30%) was noted in males and females in all treated groups at termination of dosing. The doses used in this study were 0, 100, 200 and 300 mg/kg/day. These liver weight increases were related to microsomal enzyme production. No other treatment related changes were found.

In a 90-day study in rats, dose-related irritability and urinary incontinence was observed. A dose related increase in liver weight was noted. The dosage used was up to 450 mg/kg/day.

In a 55-week study in rats, a dose-related increase in the frequency of yellow staining of the fur around the anogenital region was observed. Other findings were dry brown material around the nose or mouth and moisture around the mouth, especially soon after dosing. No compound related effects on body weight, food consumption, haematology, biochemistry or urinalysis was observed. No compound related gross pathological findings were noted. Statistically significant increases in group mean liver and kidney weights across all treated groups and a slight increase in iron positive pigment in the spleens of males at 100 mg/kg/day were noted.

In repeat dose studies in dogs of up to fifty weeks, increased salivation, emesis and dry nose and/or mouth were noted occasionally. Generally body trembling and weakness were also seen at 150mg/kg/day. Dose related frequency of occurrence of slight to moderate decrease in haemoglobin, haematocrit and total erythrocytes was noted at most intervals of analysis. Slight to moderate increase in SGPT and SGOT, alkaline phosphatase and BSP retention was noted in some dogs.

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. Data generated to date from clinical trials does not indicate an association of bupropion with hepatotoxicity in humans.

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. These doses are approximately ten and two times the maximum recommended human dose (MRHD), respectively, on a mg/m² basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately three to ten times the MRHD on a mg/m² basis); 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 positive response (2 to 3 times control mutation rate) in two of five strains in Ames bacterial mutagenicity test and an increase in chromosomal aberrations in one of three in vivo rat bone marrow cytogenetic studies.

A fertility study in rats at doses up to 300 mg/kg revealed no evidence of impaired fertility.

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PART III: CONSUMER INFORMATION

**PrZYBAN®
(bupropion hydrochloride),
sustained-release tablets
Manufacturer's Standard**

This leaflet is Part III of a three-part “Product Monograph” published when ZYBAN® was approved for sale in Canada and is designed specifically for Consumers.

This leaflet is a summary and will not tell you everything about ZYBAN. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start taking your medication even if you have taken this drug before, in case there is new information. Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:

ZYBAN is an oral prescription medication which is used in combination with a support program such as counseling to help motivated adults quit smoking.

ZYBAN can be used in combination with nicotine replacement therapy (patches, gum, lozenges, etc.).

In many cases, nicotine replacement therapy alone should be tried before trying ZYBAN.

What it does:

ZYBAN helps to reduce withdrawal symptoms and the urge to smoke.

It is not known exactly how ZYBAN works. It is thought to increase chemicals in the brain called noradrenaline and dopamine (The medicinal ingredient in ZYBAN, bupropion, is the same as in a drug called WELLBUTRIN® that is used to treat depression).

ZYBAN does not contain nicotine, unlike nicotine patches or nicotine gum.

When it should not be used?

Do not take ZYBAN if you:

- know that you are allergic to bupropion or any of the other ingredients of ZYBAN (see list of non-medicinal ingredients)
- have a seizure disorder (for example epilepsy) or have a history of seizures

- previously had seizures while taking ZYBAN or the antidepressants WELLBUTRIN® SR or WELLBUTRIN® XL
- are taking WELLBUTRIN® SR or WELLBUTRIN® XL tablets, or any other medicines that contain bupropion
- have an eating disorder, for example bulimia (binge eating) or anorexia nervosa, or have had one in the past
- are taking the antipsychotic thioridazine
- suddenly stop drinking alcohol after being a heavy drinker, or suddenly stop taking a sedative or tranquilizer medication (such as lorazepam, alprazolam) after taking them regularly
- are taking medications for Parkinson's disease or depression called monoamine oxidase inhibitor (MAOIs), or have taken them in the last 14 days.

What the medicinal ingredient is:

Bupropion hydrochloride

What the non-medicinal ingredients are:

Carnauba wax, cysteine hydrochloride, FD&C Blue No. 2 Lake, FD&C Red No. 40 Lake, hydroxypropyl-methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. Tablets are printed with edible black ink.

What dosage forms it comes in:

Tablets; 150 mg/tablet

WARNINGS AND PRECAUTIONS

IMPORTANT WARNINGS ABOUT THE RISK OF SEIZURES FOR PATIENTS TAKING ZYBAN

There is a risk of having a seizure with ZYBAN: At the maximum recommended dose of 300 mg per day, ZYBAN has been shown to cause seizures in about 1 out of every 1000 people.

For this reason, ZYBAN is not right for everyone (see section above about when ZYBAN should not be used).

If the decision is to try ZYBAN, there are precautions to be aware of to help reduce the chances of a seizure.

Do NOT take other drugs with the same medicinal ingredient (bupropion) that is in ZYBAN, such as WELLBUTRIN SR or WELLBUTRIN XL tablets (used to treat depression).

Never take more than one tablet (150 mg) of ZYBAN at one time, and never take more than two tablets total (300 mg) in a day.

BEFORE you use ZYBAN tell your doctor or pharmacist if you:

- have ever had any seizures in the past
- take other medications that may increase your chance of a seizure, including drugs for depression and some antibiotics
- are taking, or planning on taking, any prescription or over-the-counter medications, or diet aids during your therapy
- have had a serious head injury
- have kidney or liver problems
- have had a heart attack, heart problems, or high blood pressure
- are pregnant or trying to become pregnant, or if you think that you might be pregnant
- are breast feeding
- have diabetes which is treated with insulin or other medications
- regularly drink a lot of alcohol. If you are a heavy drinker and suddenly stop drinking while taking ZYBAN, you increase the chances of having a seizure.

If You Experience a Seizure

If you experience a seizure while taking ZYBAN, contact your doctor or go to a hospital emergency ward immediately. Stop taking ZYBAN, and do not start the medication at any later time, as you may suffer more seizures. In addition, you should not take any other medications that contain bupropion, such as the antidepressants WELLBUTRIN XL and WELLBUTRIN SR, due to the risk of more seizures.

Angle-Closure Glaucoma

ZYBAN can cause an acute attack of glaucoma. Having your eyes examined before you take ZYBAN could help identify if you are at risk of having angle-closure glaucoma. Seek immediate medical attention if you experience:

- eye pain
- changes in vision
- swelling or redness in or around the eye.

New or Worsened Emotional or Behavioural Problems

Particularly in the first weeks, or when doses are adjusted, a small number of people taking drugs of this type may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm, or harm to others. Your doctor should be informed of such changes immediately. Close observation by a doctor is necessary in this situation.

These symptoms can develop during treatment with ZYBAN or after stopping treatment. They can also be associated with trying to quit smoking, with or without medications to help quit.

If you, your family, or friends notice mental health changes that are unusual for you while in ZYBAN, stop taking the drug and talk to your doctor. If the symptoms are severe, seek immediate emergency help.

Pregnancy and Breastfeeding

Because of the possibility of harm to the baby, ZYBAN should only be taken during pregnancy or while breastfeeding if you and your doctor decide that the potential benefits outweigh the potential harms.

Taking ZYBAN during the first trimester is associated with a risk of heart defect in the baby. As well, some newborns whose mother took drugs of the same type as bupropion during the third trimester of pregnancy have developed complications at birth including: feeding and/or breathing difficulties, seizures, tense or floppy muscles, jitteriness, constant crying.

If you are pregnant or planning on becoming pregnant, or are breastfeeding, talk with your doctor about the risks and benefits of different anti-smoking treatment options.

Driving or Using Heavy Machinery

Do not drive a car or use heavy machinery until you know how ZYBAN affects you. ZYBAN can affect your ability to do these things safely.

ZYBAN is not recommended for use in children under 18 years of age.

Serotonin toxicity/serotonin syndrome

Taking too many tablets of ZYBAN alone or together with drugs that increase serotonin in the brain, such as antidepressants, may cause a rare but potentially life-threatening condition called serotonin toxicity/serotonin syndrome.

Symptoms include:

high body temperature (above 38°C), heavy sweating; muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination; fast heartbeat, flushing; involuntary eye movements; agitation, feeling restless.

INTERACTIONS WITH THIS MEDICATION

You should tell your doctor if you are taking or have recently taken any medications (prescription, non-prescription or natural herbal) especially:

- medicines for Parkinson's disease such as levodopa, amantadine or orphenadrine
- medicines used for epilepsy (such as carbamazepine, phenytoin, or phenobarbitone)
- the antipsychotic thioridazine
- other medications for mental illness such as haloperidol and risperidone
- antidepressants such as citalopram, paroxetine, venlafaxine

IMPORTANT: PLEASE READ

- cyclophosphamide or ifosfamide, drugs mainly used to treat cancer
- drugs called beta blockers to treat heart conditions
- medicines to regulate heart rhythm
- clopidogrel or ticlopidine, drugs used to reduce blood clots
- tamoxifen, a drug to treat breast cancer
- ritonavir or efavirenz, drugs to treat HIV infection
- sedatives or tranquilizers
- digoxin used to treat congestive heart failure and a fast heart rate or irregular heart rhythm such as atrial fibrillation sometimes called “a-fib”.

In general, drinking alcoholic beverages should be kept to a minimum or avoided completely while taking ZYBAN. Alcohol may trigger or worsen the allergic reactions. **Be sure to discuss your use of alcohol with your doctor before you begin taking ZYBAN.**

PROPER USE OF THIS MEDICATION

Usual dose:

Day	Dose
1-3	Take one 150 mg tablet of ZYBAN every morning
Day 4 to end of treatment (Generally, 7 to 12 weeks)	One 150 mg tablet twice a day – one in the morning, and one in the early evening. Be sure to take your doses at least 8 hours apart.

Never take an "extra" dose of ZYBAN.

Never take more than one tablet at a time, or more than 2 tablets in one day.

It takes about 1 week for ZYBAN to reach the right levels in your body to be effective. So, to maximize your chance of quitting, you should not stop smoking until you have taken ZYBAN for 1 week.

Your target date to stop smoking should be during the second week of taking ZYBAN.

Take ZYBAN with or without food. If you have difficulty sleeping, take the second tablet earlier in the evening (but at least 8 hours after the first tablet).

Be sure to swallow ZYBAN tablets whole. Do not crush, cut or chew the tablets - doing so may increase the chance of side effects.

ZYBAN tablets may have a distinctive odour; this is normal.

ZYBAN is usually prescribed for 7-12 weeks.

You may need to take ZYBAN for a longer period of time to prevent you from returning to previous smoking behaviour. You and your doctor will determine how long you should take it according to your individual needs.

Can ZYBAN be used at the same time as nicotine patches?

Yes, ZYBAN and nicotine patches can be used at the same time but should only be used together under the supervision of your doctor. Using ZYBAN and nicotine patches together may raise your blood pressure, sometimes severely. Tell your doctor if you are planning to use nicotine replacement therapy so that your blood pressure can be checked regularly.

Can I smoke while taking ZYBAN?

It is not dangerous to smoke and take ZYBAN at the same time. But your chances of success in breaking your smoking habit are lowered if you smoke after the date you set to quit.

Overdose

If you take too many tablets, you may increase the risk of a seizure, or other serious effects, including serotonin toxicity/serotonin syndrome (see Warnings and Precautions).

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of ZYBAN, do **NOT** double the next dose. Wait and take your next tablet at the regular time.

Remember: This medicine has been prescribed only for you. Do not give it to anybody else, as they may experience undesirable effects, which may be serious.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Whether you are taking medication to stop smoking or not, the following are symptoms you may feel: depressed, short-tempered, frustrated or angry, nervous, impatient; have difficulty concentrating. Your appetite may increase, and you may gain some weight.

Like all medications, ZYBAN can cause some side effects, although not everybody gets them.

The common side effects are mostly mild to moderate and these usually occur in the first weeks of treatment.

Common side effects of ZYBAN can include:

- difficulty sleeping
- dry mouth
- stuffy or runny nose
- dizziness

IMPORTANT: PLEASE READ

- nausea
- constipation
- disturbed concentration
- feeling anxious
- joint aches

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
<i>Symptom / effect</i>		<i>Talk with your doctor or pharmacist</i>		<i>Stop taking drug and seek immediate emergency medical attention</i>
		<i>Only if severe</i>	<i>In all cases</i>	
<i>Rare (See Warnings & Precautions)</i>	Seizures: <i>Loss of consciousness with uncontrollable shaking (convulsion).</i>			√
	Psychiatric Symptoms: <i>new or worsened emotional or behavioural problems, such as hostility, agitation, thoughts of suicide.</i>		√	√ <i>(if severe, or if involves potential for harm to self or to others)</i>
<i>Rare</i>	Allergic reaction such as: <i>redness, itching or swelling of your skin, hives, burning, stinging, swelling of the neck area, or any difficulty with breathing, not present before using this medicine.</i>			√
	Serious skin reactions such as: <i>peeling of the skin, or rash combined with blisters around the mouth, eyes or genitals.</i>			√
	Glaucoma: <i>Eye pain, change in vision, swelling or redness in or around the eye and blurred vision</i>			√
<i>Very rare</i>	Hallucinations <i>(seeing things that are not there),</i> paranoia <i>(feeling that people are against you),</i> delusions <i>(believing you are someone else).</i>		√	

IMPORTANT: PLEASE READ

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
Low sodium level in blood: tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles.		√	
Serotonin syndrome/toxicity: a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (above 38°C), or rigid muscles			√

If you think you have these side effects, it is important that you seek medical advice from your doctor straight away. ***This is not a complete list of side effects. For any unexpected effects while taking ZYBAN contact your doctor or pharmacist.***

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at:

www.healthcanada.gc.ca/medeffect

Call toll-free at: 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to:
- Canada Vigilance Program Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postal paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at:

www.healthcanada.gc.ca/medeffect

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

- Keep all medication out of the sight and reach of children.
- Store ZYBAN at 15°-25°C. Store in a dry place, protected from light.

MORE INFORMATION

You may need to read this package insert again. Please do not throw it away until you have finished your medicine. This document plus the full product monograph, prepared for health professionals can be found at <http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp> or by contacting the sponsor:

Valeant Canada LP
2150 St. Elzear Blvd., West,
Laval, QC,
H7L 4A8
1-800-361-4261

This leaflet was prepared by Valeant Canada LP
Last Revised: July 22nd, 2020