Product Monograph
Including Patient Medication Information

PrZYBAN®
Bupropion Hydrochloride Extended-Release Tablets
For oral use
150 mg
Mfr. Std.

Smoking Cessation Aid

Bausch Health, Canada Inc.
2150 St-Elzear Blvd. West
Laval, Quebec
H7L 4A8

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Recent Major Label Changes

4 Dosage and Administration, 4.1 Dosing Consideration	2023-11
7 Warnings and Precautions, Cardiovascular	2023-11
7 Warnings and Precautions, Immune	2025-05
7 Warnings and Precautions, Skin	2025-05

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1 Indications

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.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see Potential association with behavioural and emotional changes, including self-harm).

1.2 Geriatrics

Geriatrics (≥65 years of age): No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but because geriatric patients are more likely to have decreased renal function, greater sensitivity of some older individuals to bupropion cannot be ruled out (see Renal Impairment and 4 Dosage and Administration).

2 Contraindications

ZYBAN is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing of excipients, see 6 Dosage Forms, Strengths, Composition, and Packaging.
- receiving other medications that contain bupropion hydrochloride such as WELLBUTRIN XL, WELLBUTRIN SR, and CONTRAVE®, because the incidence of seizure is dose dependent (see Seizures).
- with a current seizure disorder or history of seizures (see Seizures).
- with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures (see Seizures) noted in patients treated for bulimia with the immediate release formulation of bupropion.
- undergoing abrupt withdrawal from alcohol or benzodiazepines or other sedatives.
- taking concurrent monoamine oxidase inhibitors (MAOIs) (see 9.4 Drug-Drug Interactions). Allow 14 days between discontinuation of one drug and the start of another.
- taking concurrent 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 (see 9.4 Drug-Drug Interactions). Allow 14 days between discontinuation of one drug and the start of another.

3 Serious Warnings and Precautions Box

There is an increased risk of self-harm, harm to others, suicidal thinking and behavior with bupropion. Closely monitor all treated patients for emergence of agitation-type and/or suicidal thoughts and behaviors (see Potential association with behavioural and emotional changes, including self-harm).

4 Dosage and Administration

4.1 Dosing Considerations

ZYBAN (bupropion hydrochloride) is not indicated for use in children under 18 years of age (see Potential association with behavioural and emotional changes, including self-harm). 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.

Unmasking of Brugada syndrome has been reported with bupropion. It is advised to avoid use of ZYBAN in patients with Brugada syndrome. If treatment with ZYBAN is considered in patients with Brugada syndrome and patients at risk of having Brugada syndrome (e.g., patients with unexplained syncope, patients with a family history of cardiac arrest or sudden death), an evaluation by a cardiologist should be sought prior to initiating treatment, to assess suitability of treatment and to determine the most appropriate strategy for monitoring cardiac effects (see Unmasking of Brugada syndrome).

4.2 Recommended Dose and Dosage Adjustment

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 Seizures).

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 10 Clinical Pharmacology). Whether to continue treatment with ZYBAN for periods longer than 12 weeks must be determined for individual patients.

Dosage Adjustment

- **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 7.1.1 Pregnancy). 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.

- **Geriatric Use**

Geriatric patients 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 7.1.4 Geriatrics).

- **Pediatric Use**

No data are available to Health Canada. Therefore, Health Canada has not authorized an indication for pediatric use (see Potential association with behavioural and emotional changes, including self-harm).

- **Dosage Adjustment for Patients with Impaired Hepatic and Renal Function**

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.

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 7 Warnings and Precautions).

Severe Hepatic 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 7 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 7 Warnings and Precautions and 10 Clinical Pharmacology).

Renal Impairment: 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 Renal Impairment and 10 Clinical Pharmacology).

4.4 Administration

Misuse of ZYBAN by injection or inhalation

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 (see Use of ZYBAN by injection or inhalation). The inhalation of crushed tablets or injection of dissolved

bupropion 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 (see Seizures).

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 10 Clinical Pharmacology, 14 Clinical Trials). Monitoring for treatment emergent hypertension in patients treated with the combination of ZYBAN and NTS is recommended.

4.5 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.

5 Overdose

Human Overdose Experience

In addition to those events reported under Adverse Reactions (see 8 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 extended-release formulation of bupropion; three such cases were reported during clinical trials in depressed patients. One patient ingested 3000 mg of bupropion extended-release tablets and vomited quickly after the overdose; the patient experienced blurred vision and light-headedness. A second patient ingested a "handful" of bupropion extended-release tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3600 mg of bupropion extended-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 overdosages 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 post-marketing experience (see Serotonin Toxicity / Serotonin Syndrome).

Management of Overdose

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.

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).

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal 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.

Table 2 – Description of Zyban

ZYBAN	Description
Tablets, 150 mg bupropion hydrochloride	Tablets are printed with edible black ink

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".

7 Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

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, some warnings may apply including the potential association with the occurrence of behavioural and emotional changes including self-harm (see Psychiatric).

Cardiovascular

- **Unmasking of Brugada syndrome**

There have been isolated post-marketing reports of unmasking of Brugada syndrome with bupropion. Brugada syndrome is a disorder characterized by syncope, characteristic ECG changes, such as right bundle branch block and ST segment elevation in right precordial leads, and a risk of cardiac arrest and sudden death.

It is advised to avoid use of ZYBAN in patients with Brugada syndrome. If ZYBAN is considered in patients with Brugada syndrome or in patients at risk of having Brugada syndrome (e.g., patients with unexplained syncope, patients with a family history of cardiac arrest or sudden death), an evaluation by a cardiologist should be sought prior to initiating treatment, to assess suitability of treatment and to determine the most appropriate strategy for monitoring cardiac effects. Patients should be informed about the signs and symptoms of Brugada syndrome. If unmasking of Brugada syndrome occurs,

discontinue treatment with ZYBAN.

- **Hypertension**

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 extended-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.

Dependence, Tolerance and/or Abuse Liability

- **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 (see 4.4 Administration).

Driving and Operating Machinery

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

Endocrine and Metabolism

- **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 9.4 Drug-Drug Interactions).

- **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).

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 4 Dosage and Administration; and Hepatic Insufficiency).

- **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.

Immune

- **Anaphylactic Reaction**

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 post-marketing reports of erythema multiforme 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, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

- **Cutaneous lupus erythematosus (CLE)/Systemic lupus erythematosus (SLE)**

Treatment with ZYBAN has been associated with the development of cutaneous lupus erythematosus which has resolved following withdrawal of medication. Exacerbation of systemic lupus erythematosus has also occurred. Symptoms such as arthralgia, myalgia, rash, swelling and positive autoantibodies have been observed. If any of the above effects should occur after ZYBAN treatment, ZYBAN should be discontinued, and the patient should be carefully evaluated for appropriate clinical management.

- **Hypersensitivity**

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 9.3 Drug-Behaviour Interactions).

- **Severe cutaneous adverse reactions**

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported with bupropion (see 7 Warnings and Precautions, Skin).

Neurologic

- **Seizures**

Patients should be made aware that ZYBAN (bupropion hydrochloride) Tablets contain the same active ingredient found in WELLBUTRIN SR Extended-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 2 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 extended-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 2 Contraindications), while extreme caution is recommended with other conditions, including:

- Prior seizure (see 2 Contraindications)
- History of head trauma
- Central nervous system (CNS) tumor
- 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.

- **Serotonin Toxicity / Serotonin Syndrome**

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with bupropion, including ZYBAN, particularly during combined use with other serotonergic drugs (see 9.4 Drug-Drug Interactions).
Serotonin toxicity is characterized 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 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°C and ocular clonus or inducible clonus.

If concomitant treatment with ZYBAN and serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Ophthalmologic

- **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.

Psychiatric

ZYBAN contains bupropion, a drug used to treat depression; therefore, the following precautions pertaining to this product should be considered when treating patients with ZYBAN.

- **POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**

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 (see 8 Adverse Reactions).

- **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.

- **Psychosis, Confusion, and Other Neuropsychiatric Phenomena**

In clinical trials with ZYBAN conducted in non-depressed 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 extended-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 non-depressed smokers.

Renal

- **Hyponatremia**

Hyponatremia cases have been reported very rarely with bupropion (see 8 Adverse Reactions). Caution should be exercised in patients at risk, such as geriatric patients or patients concomitantly treated with medications known to cause hyponatremia.

- **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 (see Special populations and conditions).

Skin

- **Severe cutaneous adverse reactions**

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS), are potentially life-threatening adverse drug reactions that have been reported with the use of bupropion (see 8.5 Post-Market Adverse Reactions). SCARs commonly present with one or more of the following symptoms: malaise, mucosal ulceration, extensive cutaneous rash which may be associated with pustules, exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia or neutrophilia. Discontinue ZYBAN immediately if SCARs occur.

7.1 Special Populations

7.1.1 Pregnancy

Teratogenic Effects

Teratology studies have been performed at doses up to 450 mg/kg in rats (approximately 14 times the MRHD on a mg/m^2 basis) and at doses up to 150 mg/kg in rabbits (approximately 10 times the MRHD on a mg/m^2 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 (e.g., 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 bene fits of treatment (see 4.2 Recommended Dose and Dosage Adjustment).

Labour and Delivery

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

7.1.2 Breastfeeding

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.

7.1.3 Pediatrics

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 and Health Canada has not authorized an indication for pediatric use (see Potential association with behavioural and emotional changes, including self-harm).

7.1.4 Geriatrics

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 geriatric patients (> 65 years of age) 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 Renal Impairment and 4 Dosage and Administration).

A single dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in geriatric subjects was similar to that of younger subjects; however, another single and multiple dose pharmacokinetic study has suggested that geriatric patients are at increased risk for accumulation of bupropion and its metabolites (see Special Populations and Conditions).

Of the approximately 6000 patients who participated in clinical trials with bupropion extended-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 geriatric patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8 Adverse Reactions

8.1 Adverse 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 extended release formulation of bupropion, is included in a separate section (see Other Events Observed During the Clinical Development and Post-Marketing Experience of Bupropion).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 3 - Treatment-Emergent Adverse Event Incidence in the Dose-Response Trial*

	ZYBAN 100-300mg/day (n=461) %	PLACEBO (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

	ZYBAN 100-300mg/day (n=461) %	PLACEBO (n=150) %
Respiratory		
Bronchitis	2	0
Skin		
Pruritus	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 4 - Treatment-Emergent Adverse Event Incidences (%) in the Comparative Trial

	ZYBAN 300mg/day (n=243) %	Nicotine Transdermal System (NTS) 21mg/day (n=243) %	ZYBAN and NTS (n=244) %	Placebo (n=159) %
Body (General)				
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

	ZYBAN 300mg/day (n=243) %	Nicotine Transdermal System (NTS) 21mg/day (n=243) %	ZYBAN and NTS (n=244) %	Placebo (n=159) %
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

	ZYBAN 300mg/day (n=243) %	Nicotine Transdermal System (NTS) 21mg/day (n=243) %	ZYBAN and NTS (n=244) %	Placebo (n=159) %
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.

8.5 Post-Market Adverse Reactions

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 Post-Marketing 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 Seizures).

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

Adverse events for which frequencies are provided below occurred in clinical trials with bupropion extended 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 extended 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 post-marketing experience with bupropion. Only those adverse events not previously listed for extended-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 Brugada syndrome, cardiovascular disorder, complete AV block, extrasystoles, hypotension, hypertension (in some cases severe; see Cardiovascular), myocardial infarction, phlebitis, and pulmonary embolism.

Cutaneous lupus erythematosus (CLE) and aggravation of systemic lupus erythematosus (SLE)

Evidence of a causal relationship between bupropion and CLE or aggravation of SLE was found in post-marketing adverse event reports.

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, irritability and panic attack. Panic attacks and other panic events (panic reaction, panic disorder with or without agoraphobia) have been reported in patients treated with ZYBAN, both with and without pre-existing psychiatric disorder.

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.

Dysphemia: Post-marketing reports suggest a link between dysphemia and ZYBAN. Symptoms typically resolve upon discontinuation and may reappear with rechallenge. Patients with a history of dysphemia may experience exacerbation of symptoms.

Respiratory

Rare was bronchospasm.

Also observed was pneumonia.

Skin/Hypersensitivity

Frequent was sweating.

Infrequent was acne and dry skin.

Rare was maculopapular rash and very rare was acute generalised exanthematous pustulosis (AGEP).

Also observed were alopecia, angioedema, drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme, exfoliative dermatitis, hirsutism, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). 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.

9 Drug Interactions

9.1 Serious Drug Interactions

Serious drug interactions with ZYBAN include:

- concomitant medicines that contain bupropion hydrochloride (e.g., WELLBUTRIN XL, WELLBUTRIN SR, and CONTRAVE);
- monoamine oxidase inhibitors (MAOI);
- medicines that contain thioridazine.

See 2 Contraindications for details.

9.2 Drug Interactions Overview

In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by Cytochrome P450 llB6 (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.

9.3 Drug-Behaviour Interactions

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 Seizures).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports (C) or studies (CT), or potential interactions (T) due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5- Established or Potential Drug-Drug Interactions with ZYBAN

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs Metabolized by CYP2D6 including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics	CT	↓ CYP2D6 isoenzyme Bupropion and hydroxybupropion are inhibitors of the CYP2D6 isoenzyme *in vitro*. In 15 male subjects (aged 19 to 35 years) who were extensive metabolizers of CYP2D6, 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 t1/2 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 therapy with drugs predominately metabolized by CYP2D6 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 medications with a narrow therapeutic index.
Tamoxifen (a pro-drug requiring metabolic activation by CYP2D6)	T	↓ efficacy of tamoxifen	Co-administration of Tamoxifen with strong CYP2D6 inhibitors such as bupropion can lead to reduced plasma concentrations of a primary active metabolite (endoxifen) which may result in reduced efficacy of tamoxifen. Bupropion

Proper/Common name	Source of Evidence	Effect	Clinical comment
			should not be used in combination with tamoxifen and other treatment options should be considered (see Potential for reduced efficacy of Tamoxifen).
Citalopram	CT	↑ C_{max} and AUC of citalopram	In 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.
Ritonavir/Lopinavir/ Efavirenz	CT	↓ bupropion AUC 20 - 80% ↓ bupropion AUC 55% 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 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).	Patients receiving ritonavir, lopinavir or efavirenz 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/ lopinavir and efavirenz have not been studied.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Co-administration of Thioridazine Contraindicated	T	↓ inhibition of thioridazine metabolism	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 WELLBUTRIN XL is contraindicated (see 2 Contraindications).
MAO Inhibitors	T	↑ acute toxicity of bupropion	Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor, phenelzine (see 2 Contraindications)
Cimetidine	CT	↑ combined threohydro and erythrobupropion AUC (16%) and C_{max} (32%)	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 ZYBAN tablets with and without 800 mg of cimetidine. A single dose of cimetidine had no effect on single dose pharmacokinetic

Proper/Common name	Source of Evidence	Effect	Clinical comment
			parameter estimates for bupropion, or hydroxybupropion, but caused a small statistically significant increase in the combined threohydro and erythrobupropion AUC (16%) and C_{max} (32%).
Lamotrigine	CT	↑ AUC of its metabolite	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	CT	↑ incidence of neuropsychiatric adverse experiences	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.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Clopidogrel and Ticlopidine	CT	↑ plasma concentrations of bupropion and ↓ concentrations of hydroxybupropion 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.	Both clopidogrel and ticlopidine have been shown to significantly inhibit CYP2B6-catalysed bupropion hydroxylation. This may affect the efficacy of bupropion and may also increase the risk of concentration-dependent adverse events of bupropion, such as seizures (see Seizures). Patients receiving either clopidogrel or ticlopidine are likely to require dose adjustments of bupropion.
Digoxin	CT	↓ digoxin AUC_{0-24h} and increases renal clearance A clinical report suggests that when administered ~24 hours before digoxin, bupropion (extended-release, 150 mg) decreases digoxin AUC_{0-24h} 1.6-fold and increases renal clearance 1.8-fold in healthy volunteers.	Co-administration of digoxin with bupropion may decrease digoxin levels. Monitor digoxin levels in patients treated concomitantly with bupropion and digoxin. Clinicians should be aware that digoxin levels may rise on discontinuation of bupropion and the patient should be monitored for possible digoxin toxicity.
Drugs that Predispose Patients to Seizures	T		Concurrent administration of ZYBAN Tablets with agents that lower seizure threshold (e.g., antipsychotics, other antidepressants, theophylline, lithium, systemic steroids, etc.) should be undertaken only with extreme caution (see Seizures). Low initial dosing and gradual dose increases should be employed.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Other Drugs with CNS Activity	T		The risk of using ZYBAN in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZYBAN and such drugs is required.
Transdermal Nicotine Interaction	CT		(see Cardiovascular) 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.
SSRIs/SNRIs	C	↑ Serotonin	Increased risk of Serotonin toxicity (see Serotonin Toxicity / Serotonin Syndrome).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Food does not have a clinically relevant effect on bupropion hydrochloride pharmacokinetics, therefore ZYBAN may be taken with or without food.

9.6 Drug-Herb Interactions

Interactions with herb have not been established.

9.7 Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. This is due to lack of specificity of some screening tests. False-positive test results may occur even following discontinuation of bupropion therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines.

10 Clinical Pharmacology

10.1 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.

10.2 Pharmacodynamics

In vitro, bupropion and its major metabolites had essentially no affinity for β-adrenergic, dopaminergic, GABA, benzodiazepine, 5HT1A, glycine and adenosine receptors, and only weakly inhibited α-adrenergic receptors in rat brain, α2-adrenergic, 5HT2, and muscarinic cholinergic receptors. High concentrations of bupropion and its major metabolites did not inhibit MAO-A or MAO-B activity. Bupropion and its major metabolites had no significant affinity for the 5HT transport system.

Large i.v. doses of bupropion had no sustained adverse effects on the cardiovascular system of dogs (13-50 mg/kg cumulative) and cats (18.5 mg/kg). Transient (<10 min) significant, dose-dependent decreases in mean arterial pressure and cardiac output with variable effects on heart rate were observed following bolus IV injections; the effects were much greater following bolus administration than following equivalent infused doses. The effects were most likely related to the transient high plasma levels (approximately 10-fold higher than both therapeutic plasma levels in man and plasma levels associated with the mouse antidepressant ED_{50}) and the local anesthetic-like activity. At all dose levels studied, effects on the ECG were entirely related to heart rate; there were no changes in the PR, QRS or QTC intervals. No arrhythmias were observed.

Oral administration of high doses did not produce deleterious cardiovascular effects in conscious dogs (25 mg/kg) and normotensive rats (25-50 mg/kg). Weak, transient dose-dependent effects on the pressor responses to exogenous NA and tyramine were seen in anaesthetized dogs; bupropion was approximately 10-fold weaker than imipramine in this regard. The compound essentially lacked sympathomimetic actions in dogs and cats.

10.3 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 (±% CV) of about 21 hours (±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 Extended-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 (Cmax) values were 91 and 143 ng/mL from two single dose (150 mg) studies. At steady state, the mean Cmax 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 extended-release bupropion tablets are taken with food. When taken following food, peak plasma concentration of bupropion (Cmax) 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.

- **Food Effect:** Food increased C_{max} and AUC of bupropion by 11% and 17%, respectively, indicating that there is no clinically significant food effect.

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 (Vss/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 IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.

Plasma concentrations of the metabolites exceed those of the parent drug and may be clinically important. Factors or conditions altering metabolic capacity or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450 IIB6 isoenzyme (see 9.4 Drug-Drug Interactions). Although bupropion is not metabolized by cytochrome P450 IID6, there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see Drugs Metabolized by Cytochrome P450 IID6).

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 non-smokers. 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 non-smokers.

Elimination

The mean (±% CV) apparent clearance (Cl/F) estimated from two single dose (150 mg) studies are 135 (±20%) and 209 L/hr (±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 (±23%). The mean elimination half life (± SD) of bupropion after chronic dosing is 21 (±9) hours. Estimates of the half lives of the metabolites determined from a multiple dose study were 20 hours (±25%) for hydroxybupropion, 37 hours (±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%.

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.

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 geriatric 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 geriatric patients are at increased risk for accumulation of bupropion and its metabolites see 7.1.4 Geriatrics).
- **Sex:** 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 7 Warnings and Precautions, see 4.2 Recommended Dose and Dosage Adjustment).

- **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.
- **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.

11 Storage, Stability, and Disposal

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

Part 2: Scientific Information

13 Pharmaceutical Information

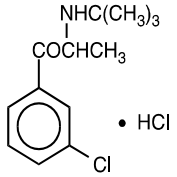
Drug Substance

Proper name: Bupropion hydrochloride

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

Molecular formula and molecular mass: $C_{13}H_{18}ClNO \cdot HCl$ 276.2 Daltons

Structural formula:



Physicochemical properties:

Description: Bupropion hydrochloride is a white powder with slight characteristic odour.

Solubility: In water of 312 mg/mL at 25ºC.

14 Clinical Trials

14.1 Clinical Trials by Indication

Aid to Smoking Cessation

Table 6 - Summary of Patient Demographics for Clinical Trials in Aid to Smoking Cessation

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
First and second studies	placebo controlled, double blind trials in nondepressed chronic cigarette smokers	Treated for 7 weeks with one of three doses of ZYBAN (100, 150, or 300 mg/day) or placebo	1,508 ≥15 cigarettes per day	N/A	N/A
Third study	placebo-controlled, double-blind trial of nondepressed chronic cigarette smokers	Up to 1 year	432 ≥15 cigarettes per day	N/A	N/A

Table 7 - Results of study # 1 in Aid to Smoking Cessation

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
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.	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.	Results show 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 (see table 8)

Table 8 - 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 ≤ 0.05).

Table 9 - Results of study # 2 in Aid to Smoking Cessation

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
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.	The second study was a comparative trial conducted at four clinical centers. Four treatments were evaluated: ZYBAN 300 mg/day, HABITROL® (nicotine transdermal system) (NTS) 21 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.	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 (see table 10).

Table 10 - 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.

Table 11 - Results of study # 3 in Aid to Smoking Cessation

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
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.	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.

16 Non-Clinical Toxicology

General 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.

Carcinogenicity

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/m^2 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/m^2 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.

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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrZYBAN®

Bupropion Hydrochloride Extended-Release Tablets

This patient medication information is written for the person who will be taking **ZYBAN**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **ZYBAN**, talk to a healthcare professional.

Serious warnings and precautions box

New or worsened emotional or behaviour problems:

- When you first start taking ZYBAN or when your dose is adjusted, you may experience new or worsened feelings of agitation, hostility, anxiety, or impulsivity.
- It is important that you and your healthcare professional talk regularly during your treatment about how you are feeling.
- You may find it helpful to tell a relative or close friend that you are taking this medicine to help you to quit smoking. Ask them to read this leaflet. You might ask them to tell you if they are worried about changes in your behaviour.
- If you experience changes in your behaviour, tell your healthcare professional right away.

Self-harm or Suicide

- Bupropion can increase the risk of suicidal thoughts or actions.
- If you have thoughts of harming or killing yourself at any time, tell your healthcare professional or go to a hospital right away. You will be closely monitored by a healthcare professional in this situation.

What ZYBAN is used for:

ZYBAN is used in motivated adults to help quit smoking when combined with:

- a support program such as counselling; or
- a nicotine replacement therapy (e.g., patches, gum, lozenges, etc.).

A nicotine replacement therapy alone should be considered before trying ZYBAN.

How ZYBAN works:

It is not known exactly how ZYBAN works. It is thought to increase chemicals in the brain called noradrenaline and dopamine. This may help reduce withdrawal symptoms and the urge to smoke.

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

The ingredients in ZYBAN are:

Medicinal ingredient: bupropion hydrochloride.

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. Tablets are printed with edible black ink.

ZYBAN comes in the following dosage forms:

Tablets; 150 mg of bupropion hydrochloride.

Do not use ZYBAN if:

- you know that you are allergic to bupropion or any of the other ingredients of ZYBAN.
- you are taking any other medicines which contain bupropion hydrochloride, such as WELLBUTRIN XL, WELLBUTRIN SR, or CONTRAVE®.
- you have been diagnosed with a seizure disorder (for example epilepsy) or have a history of seizures or fits.
- you previously had seizures while taking ZYBAN or the antidepressants WELLBUTRIN® SR or WELLBUTRIN® XL.
- you have, or have had, an eating disorder, such as:
  - bulimia (binge eating and then purging so you don't gain weight);
  - anorexia (eating very little).
- you are a heavy drinker, have recently stopped drinking alcohol, and have withdrawal symptoms.
- you have suddenly stopped taking benzodiazepines or other sedatives (medicines used to treat anxiety and sleep disorders) and have withdrawal symptoms.
- you are taking or have recently taken in the last 14 days medications called monoamine oxidase inhibitors (MAOIs), for depression (such as phenelzine, moclobemide, and tranylcypromine) or for Parkinson's disease (such as selegiline).
- you are taking or have recently taken in the last 14 days thioridazine (an antipsychotic medicine that is typically used to treat schizophrenia and psychosis).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZYBAN. Talk about any health conditions or problems you may have, including if you:

- are at a higher risk of seizures. This includes if you:
  - are taking other medicines containing bupropion, such as WELLBUTRIN XL, WELLBUTRIN SR, and CONTRAVE®.
  - have ever had any fits or seizures in the past.
  - have had a serious head injury.
  - have or have had a tumour in your brain or spinal cord.
  - have liver problems.
  - are addicted to opioids, cocaine or other drugs that stimulate your central nervous system.

- excessively drink alcohol. It is best not to drink alcohol at all. If you drink a lot of alcohol and suddenly stop, you may increase your risk of having a seizure. Be sure to discuss your use of alcohol with your healthcare professional before you start taking ZYBAN.
- have diabetes and take insulin or other medicines to control your blood sugar.
- take other medications that may increase your risk of having a seizure, such as:
  - medicines used to treat depression or other mental disorders (e.g., serotonergic agents);
  - medicines used to treat psychotic symptoms;
  - medicines used to treat malaria;
  - lithium, a medicine used to treat bipolar disorder;
  - amantadine, a medicine used to treat Parkinson's Disease;
  - theophylline, a medicine used to treat asthma and other lung diseases;
  - steroids, which are medicines used to treat inflammation;
  - some antibiotics (e.g., quinolones);
  - over-the-counter stimulants (e.g., diphenhydramine, dextromethorphan, or pseudoephedrine); or
  - diet aids.

- have bipolar disorder.
- are using nicotine patches to help you stop smoking.
- have recently had a heart attack or have heart disease.
- are taking tamoxifen, a medicine used to treat breast cancer.
- are 65 years of age or older.
- are taking medicines that are known to lower the level of sodium in your blood (e.g., thiazide diuretics, a type of "water pill").
- have kidney problems.
- have or have had a speech disorder where you stammer or stutter (dysphemia). Taking ZYBAN may cause your speech disorder to come back or worsen.

Other warnings you should know about:

ZYBAN can cause serious side effects including:

- **Seizures** (fits): Your risk of seizures increases when you take ZYBAN, even if you have never had one before. Factors that increase your risk of seizures while taking ZYBAN:
  - when your dose of ZYBAN increases;
  - if you do not take ZYBAN as prescribed;
  - if you take certain medicines at the same time;
  - if you are already at higher than usual risk of seizures.

- **Serotonin toxicity (also known as serotonin syndrome):** ZYBAN can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take ZYBAN with certain anti-depressants or migraine medications.

  Serotonin toxicity symptoms include:
  - fever, sweating, shivering, diarrhea, nausea, vomiting;
  - muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
  - fast heartbeat, changes in blood pressure;

- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

- **Severe allergic reactions:**
  - ZYBAN XL may cause an allergic reaction. Symptoms may include skin rash, hives, swelling of the face or throat, muscle pain, joint pain, difficulty breathing, severe skin reactions, chest pain, or fever.
  - If you have an allergic reaction while taking ZYBAN XL, your symptoms may not go away even after you stop taking it.

- **Severe skin reactions:** Taking ZYBAN may cause serious skin reactions. This includes Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening, and erythema multiforme. The following symptoms may be related to these skin reactions:
  - Early warnings for patients:
    - fever
    - severe skin rash
    - swelling, swollen lymph glands
    - flu-like feeling
    - itching
    - body aches
    - blisters and peeling skin that may start in and around the mouth, nose, eyes, and genitals and spread to other areas of the body
  - Later developments:
    - yellow skin or eyes
    - shortness of breath
    - dry cough
    - chest pain or discomfort
    - feeling thirsty
    - urinating less often, less urine

  Stop taking ZYBAN and contact your healthcare professional immediately if you experience these symptoms.

- **Systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE):** ZYBAN has been associated with new or worsening symptoms in patients susceptible to SLE and CLE. These are autoimmune diseases where your body's immune system attacks your own tissues and organs. Talk to your healthcare professional right away if you have blotchy rashes mainly on the face, fatigue, joint pain, swelling in the joints, muscle pain, rash, swelling, fever, nausea, or loss of appetite.

- **Angle-closure glaucoma** (eye pain caused by increased pressure in the eyes): 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. Get immediate medical help if you experience:

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

- **Brugada syndrome (serious heart problem):** ZYBAN may reveal a hidden heart problem you did not know you had, a problem called Brugada syndrome. Brugada syndrome can be serious and cause sudden death. Get immediate medical help if you experience fainting, dizziness, heart palpitations or abnormal heartbeat while taking ZYBAN.

  Before you start taking ZYBAN, tell your healthcare professional if you:
  - have Brugada syndrome.
  - have unexplained fainting, or a family history of Brugada syndrome or unexplained sudden death before 45 years of age. This could mean you may have Brugada syndrome.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Alcohol: ZYBAN lowers your alcohol tolerance. This means you may feel the effects of alcohol when taking less alcohol than usual. Drinking alcohol while taking ZYBAN may increase your risk of having seizures and allergic reactions. It is best not to drink alcohol at all while taking ZYBAN to avoid side effects.

Misuse: ZYBAN is intended for oral use only. Taking ZYBAN by any other route may lead to seizure, overdose or even death.

Pregnancy:

- If you are pregnant, your healthcare professional will determine if ZYBAN is right for you. They will also discuss the risks of birth defects and complications after birth if you take ZYBAN during pregnancy.
- If you have been prescribed ZYBAN during pregnancy, be ready to seek immediate medical help for your newborn if they:
  - have trouble breathing or feeding;
  - have muscle stiffness, or floppy muscles (like a rag doll);
  - have seizures (fits);
  - are shaking (jitteriness);
  - are constantly crying.
- Tell your healthcare professional **right away** if you become pregnant while taking ZYBAN. It is very important that you do **not** stop taking ZYBAN without first consulting with your healthcare professional.

Breastfeeding: ZYBAN passes into breastmilk and could harm a breastfed baby. You and your healthcare professional will decide if you should take ZYBAN or breastfeed. You should not do both.

Urine drug screening test: If you take a urine drug screening test, ZYBAN may give a positive test result for amphetamines. Tell the laboratory technician that you are taking ZYBAN. They can do a more specific drug screening test for you.

Driving or using machines: ZYBAN may impair your ability to do tasks requiring judgement, thinking, or motor skills. You should not drive or use machines until you know how ZYBAN affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious drug interactions:

Serious drug interactions with ZYBAN include:

- medicines that contain bupropion hydrochloride (e.g., WELLBUTRIN XL, WELLBUTRIN SR, and CONTRAVE);
- monoamine oxidase inhibitors (MAOI) taken within the last 14 days, which are used to treat depression (e.g., phenelzine, moclobemide, and tranylcypromine);
- medicines that contain thioridazine taken within the last 14 days, which are typically used to treat schizophrenia and psychosis.

Do not take ZYBAN if you are taking any of these medicines. Ask your healthcare professional if you are unsure.

The following may also interact with ZYBAN:

- medicines used to treat depression and other mental illnesses, such as citalopram, paroxetine, venlafaxine, nortriptyline, imipramine, desipramine, fluoxetine, sertraline, haloperidol, or risperidone.
- medicines used to treat Parkinson's Disease, such as levodopa, amantadine, or orphenadrine.
- medicines used to prevent epilepsy or seizures, such as carbamazepine, phenytoin, or phenobarbital.
- medicines used to treat cancer, such as cyclophosphamide or ifosfamide.
- medicines used to treat HIV infection, such as ritonavir, lopinavir, or efavirenz.
- beta blockers, which are used to lower your blood pressure. This includes metoprolol, bisoprolol, or carvedilol.
- medicines used to regulate your heart rhythm, such as propafenone, or flecainide.
- medicines used to reduce blood clots, such as ticlopidine or clopidogrel.
- nicotine patches, which are used to help you stop smoking.
- tamoxifen, a medicine used to treat breast cancer.
- digoxin, a medicine used to treat various heart conditions.
- theophylline, a medicine used to treat asthma and other lung diseases.
- lithium, a medicine used to treat bipolar disorder.
- steroids, which are used to treat inflammation, such as prednisone.
- alcoholic beverages.

How to take ZYBAN:

- **Never take an "extra" dose of ZYBAN.**

- **Never take more than one tablet at a time, or more than 2 tablets in one day.**
- ZYBAN can be taken with or without food.
- Swallow ZYBAN tablets whole. Do **not** crush, cut or chew the tablets.
- If you have trouble sleeping while taking ZYBAN, take the second tablet earlier in the evening (but at least 8 hours after the first tablet).
- ZYBAN tablets may have a distinctive odour; this is normal.
- It takes about 1 week for ZYBAN to reach the right levels in your body to be effective. Therefore, 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.

Using ZYBAN at the same time as nicotine patches:

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

Smoking while taking ZYBAN:

It is not dangerous to smoke while taking ZYBAN. If you continue to smoke after the date you set to quit while taking ZYBAN this will lower your chances of success in breaking your smoking habit.

Usual dose:

Your healthcare professional will determine the right dose for you. The usual adult dose is listed in this table:

Day	Dose
Day 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.

ZYBAN is usually taken for 7 to 12 weeks. You may need to take ZYBAN for a longer period of time to prevent you from returning to your previous smoking behaviour. You and your healthcare professional will decide how long you should take ZYBAN according to your individual needs.

Overdose:

The symptoms of an overdose include:
- drowsiness;
- fainting;
- respiratory arrest (breathing stops);
- amnesia (loss of memories);
- seizures;

- irregular heartbeat, which can be life-threatening;
- serotonin syndrome, which is a serious condition that can be life-threatening. See the **Serious side effects and what to do about them** table for more details.

If you think you, or a person you are caring for, have taken too much ZYBAN, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you forget or miss a dose of ZYBAN skip the missed dose and take the next dose as scheduled. **Do not double the dose to make up for the missed dose.**

Possible side effects from using ZYBAN:

These are not all the possible side effects you may have when taking ZYBAN. If you experience a side effect not listed here, tell your healthcare professional.

Side effects may include:

- difficulty sleeping,
- dry mouth,
- stuffy or runny nose,
- dizziness,
- nausea,
- constipation,
- trouble concentrating,
- feeling anxious,
- joint aches.

Even if you do not take medicine to help you quit smoking you might feel depressed, short-tempered, frustrated, angry, nervous and impatient while trying to quit. Your appetite might also increase, and you may gain weight.

Serious side effects and what to do about them:

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Panic attacks: sudden intense fear and discomfort			√
Rare			

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Angle-closure glaucoma (eye condition that can cause damage to the optic nerve): increased pressure in your eyes, sudden eye pain, eye and head pain, swelling or redness in or around the eye, hazy or blurred vision, sudden loss of sight.			√
New or worsened emotional or behavioural problems: feeling angry, aggressive, worried, agitated, hostile or impulsive, feeling violent, feeling like you are not yourself or that you are less inhibited.		√	
Seizures (fits): loss of consciousness with uncontrollable shaking.			√
Severe allergic reaction: redness, itching, blistering, or swelling of your skin, hives, burning, stinging, swelling of the lips, face, eyes or tongue, difficulty breathing or swallowing, wheezing, shortness of breath, collapse, severe muscle or joint pains, or loss of consciousness.			√
Severe skin reactions: any combination of itchy skin rash, redness, blistering and peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands, joint pain, yellowing of the skin or eyes, dark urine, shortness of breath, chest pain or discomfort, feeling thirsty, urinating less often, less urine.			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Systemic lupus erythematosus (SLE) and **Cutaneous lupus erythematosus (CLE):** red blotchy rash mainly on the face which may be accompanied by fatigue, pain or swelling in joints, muscle pain, fever, nausea, or loss of appetite.		√	
Thoughts of death or suicide: thoughts or actions about hurting or killing yourself or other people.			√
Very rare			
Hallucinations, delusions or paranoia (sensing or believing thing that are not there).		√	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness, fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse, or heart palpitations.	√		
Hyponatremia (low blood sodium): tiredness, weakness, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizure, or coma.		√	
Liver disorders (including hepatitis and jaundice): yellowing of the skin or eyes, dark urine, pale stools, abdominal pain, nausea, vomiting, loss of appetite, or itching.		√	
Mania: elevated or irritable mood, talking fast, taking more risks, needing less sleep, or racing thoughts.		√	
Poor blood sugar control	√		
Serotonin toxicity (also known as serotonin syndrome): a feeling of agitation or restlessness, flushing, muscle twitching, involuntary eye			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
movements, heavy sweating, high body temperature (above 38°C), or rigid muscles.			
Unknown			
Brugada syndrome (serious heart problem): dizziness, fainting, fast heartbeat, palpitations, abnormal heartbeat, seizures (fits), abnormal breathing while sleeping.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Keep out of reach and sight of children.

If you want more information about ZYBAN:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.bauschhealth.ca, or by calling 1-800-361-4261.

This leaflet was prepared by:

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