Product Monograph

Including Patient Medication Information

PrWELLBUTRINâ SR

Bupropion Hydrochloride Sustained-Release Tablets

For oral use

150 mg

Mfr. Std.

Antidepressant

Bausch Health, Canada Inc.
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Laval, Quebec
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Recent Major Label Changes

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Part 1: Healthcare Professional Information

1 Indications

WELLBUTRIN SR is indicated for:

- the symptomatic relief of major depressive illness. The effectiveness of WELLBUTRIN SR in long-term use (greater than 8 weeks) has not been evaluated in controlled trials.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of WELLBUTRIN SR in pediatric patients have not been established; 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

WELLBUTRIN SR (bupropion hydrochloride) 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, see 6 Dosage Forms, Strengths, Composition, and Packaging.
- receiving WELLBUTRIN XL, ZYBAN, CONTRAVE or any other medications that contain bupropion hydrochloride 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 (MAO) inhibitors (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 Precaution Box

- Increased risk of self-harm, harm to others, suicidal thinking and behavior with antidepressants use. Closely monitor all antidepressant-treated patients for clinical worsening and 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

WELLBUTRIN SR (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).

Unmasking of Brugada syndrome has been reported with bupropion. It is advised to avoid use of WELLBUTRIN SR in patients with Brugada syndrome. If treatment with WELLBUTRIN SR 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).

When switching patients from WELLBUTRIN XL (WXL) extended-release tablets to WELLBUTRIN SR (WSR), give the same total daily dose when possible (for example 300 mg WXL once a day may be switched to 150 mg WSR twice daily). WELLBUTRIN SR should never be taken concurrently with WELLBUTRIN XL or other medications containing bupropion.

4.2 Recommended Dose and Dosage Adjustment

The usual recommended dose of sustained release bupropion hydrochloride is 150 mg/day given once daily. As with all antidepressants, the full antidepressant effect of WELLBUTRIN SR may not be evident until several weeks of treatment. In patients who are not responding to a dose of 150 mg/day, the dose may be increased up to a maximum of 300 mg/day. Dose increases should occur at intervals of at least one week. In order to minimize the risk of seizures (see Seizures), single doses of WELLBUTRIN SR must not exceed 150 mg**.** Doses of WELLBUTRIN SR greater than 150 mg/day should be administered b.i.d. preferably with at least 8 hours between successive doses.

Hepatic Impairment

- **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 with WELLBUTRIN SR should be initiated at the lowest recommended dose. Maintenance dose may be adjusted according to clinical response and tolerance. Caution should be exercised as there is no clinical experience with WELLBUTRIN SR in hepatically impaired patients (see also Hepatic/Biliary/Pancreatic).

- **Severe Hepatic Impairment**

Given the risks associated with both peak bupropion levels and drug accumulation, WELLBUTRIN SR 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 Hepatic/Biliary/Pancreatic). The dose should not exceed 150 mg every day or 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 Hepatic Insufficiency and Hepatic/Biliary/Pancreatic).

Renal Impairment

WELLBUTRIN SR should be used with caution in patients with renal impairment due to the potential for drug accumulation, and a reduced frequency and/or dose should be considered (see Renal).

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.

Treatment of Pregnant Women During the Third Trimester

Post-marketing reports indicate that some neonates exposed to WELLBUTRIN SR, 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 WELLBUTRIN SR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering WELLBUTRIN SR in the third trimester.

Geriatrics or Debilitated Patients

No pharmacokinetic or therapeutic trials have been conducted to systematically investigate dose requirements in patients who are geriatric or debilitated (see 7.1.4 Geriatrics). As such patients may have reduced clearance of bupropion and its metabolites, and/or increased sensitivity to the side-effects of CNS active drugs, treatment with bupropion hydrochloride should be initiated at the lowest recommended dose (100 mg/day).

Pediatrics

WELLBUTRIN SR is not indicated for use in children under 18 years of age (see 1.1 Pediatrics and Potential association with behavioural and emotional changes, including self-harm)**.**

4.4 Administration

Patients should be advised to swallow WELLBUTRIN SR 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 Misuse of WELLBUTRIN SR 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).

4.5 Missed Dose

WELLBUTRIN SR 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

In addition to those events reported under 8 Adverse Reactions, overdose has resulted in symptoms including drowsiness, loss of consciousness, status epilepticus, and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias; cases of fatal outcome have been reported. QTc prolongation has also been reported but was generally seen in conjunction with QRS prolongation and increased heart rate. Three overdoses with WELLBUTRIN SR (bupropion hydrochloride) occurred during clinical trials. One patient ingested 3000 mg of WELLBUTRIN SR tablets and vomited quickly after the overdose; the patient experienced blurred vision and light-headedness. A second patient ingested a "handful" of WELLBUTRIN SR tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3,600 mg of WELLBUTRIN SR tablets and a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess". None of the patients experienced further sequelae.

The information included in the remainder of this section is based on the clinical experience with overdosage of the immediate release formulation of bupropion. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of WELLBUTRIN 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 WELLBUTRIN, 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 WELLBUTRIN alone included hallucinations, loss of consciousness, and sinus tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when WELLBUTRIN was part of multiple drug overdoses.

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

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with bupropion in association with overdose. These cases include chronic administration at supratherapeutic doses (doses just above the maximum recommended daily dose, e. g. 600-800 mg). Treatment with WELLBUTRIN SR should be discontinued if patients develop a combination of symptoms possibly including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma and supportive symptomatic treatment should be initiated. If concomitant treatment with WELLBUTRIN SR or serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see Serotonin Toxicity/ Serotonin Syndrome, and 9.4 Drug-Drug Interactions).

Management of Overdose

In the event of overdose, hospitalization 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 WELLBUTRIN SR, 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 centre for additional information on the treatment of any overdose. Telephone numbers for certified poison control centres 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	Tablets 150 mg	Carnauba Wax, Cysteine Hydrochloride, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Titanium Dioxide, FD&C Blue No. 2 Lake, FD&C Red No. 40 Lake, Polysorbate 80 and Edible Black Ink

Description

WELLBUTRIN SR 150 mg tablets are supplied as purple, round, biconvex, film-coated tablets printed with 'WELLBUTRIN SR 150' in black ink. WELLBUTRIN SR 150 mg tablets are supplied in bottles of 60 tablets.

7 Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

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 WELLBUTRIN SR in patients with Brugada syndrome. If WELLBUTRIN SR 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 WELLBUTRIN SR.

- **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 the sustained-release formulation of bupropion (ZYBAN® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained- release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained- release bupropion, 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 limited clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. In a study of depressed inpatients with stable heart failure, bupropion was associated with a rise in supine blood pressure, resulting in discontinuation of two patients for exacerbation of baseline hypertension.

Dependence, Tolerance, and/or Abuse Liability

- **Misuse of WELLBUTRIN SR by injection or inhalation**

WELLBUTRIN SR 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

- **Decreased Appetite and Weight**

In clinical trials WELLBUTRIN SR was associated with dose-related weight loss. In eight-week, controlled trials mean weight loss for trial completers was 0.1 kg for placebo, 0.8 kg for WELLBUTRIN SR 100 mg/day, 1.4 kg at 150 mg/ day, and 2.3 kg at 300 mg/day. If weight loss is a major presenting sign of a patient's depressive illness, the potential anorectic and/or weight reducing effect of bupropion hydrochloride should be considered.

- **Drugs Metabolized by Cytochrome P450 (CYP2D6)**

Drugs which require metabolic activation by CYP2D6 in order to be effective (e.g. tamoxifen), may have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Therefore, bupropion should not be used in combination with tamoxifen and other treatment options should be considered (see 9 Drug Interactions).

Hepatic/Biliary/Pancreatic

- **Hepatic Impairment**

The results of two single dose pharmacokinetic studies indicate that 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, WELLBUTRIN SR 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.

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 Hepatic Impairment 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 requiring medical treatment have been reported in clinical trials with bupropion at a rate of 1-3 per thousand. In addition, there have been rare spontaneous post marketing reports of erythema multiforme, and anaphylactic shock associated with bupropion. In uncontrolled and controlled clinical trials, skin disorders, primarily rashes, pruritus, and urticaria, lead to discontinuation of 1.5% and 1.9 %, respectively of bupropion-treated subjects. A patient should stop taking WELLBUTRIN SR 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 WELLBUTRIN SR 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 WELLBUTRIN SR treatment, WELLBUTRIN SR should be discontinued and the patient should be carefully evaluated for appropriate clinical management.

- **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 Skin).

- **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 Alcohol Interactions).

Neurologic

- **Seizures**

Patients should be made aware that WELLBUTRIN SR contains the same active ingredient (bupropion hydrochloride) as ZYBAN, ZYBAN, CONTRAVE and WELLBUTRIN XL. WELLBUTRIN SR should NOT be administered to patients already receiving a product containing bupropion hydrochloride (see 2 Contraindications).

Data for WELLBUTRIN SR Tablets revealed a seizure incidence of approximately 0.1% (3 of 3,100 patients followed prospectively) in patients treated at the recommended dose range of 100 to 300 mg/day. The incidence of seizures increased to 0.4% (4/1000), above the recommended dose, at 400 mg/day. Data for the immediate release bupropion revealed a seizure incidence of approximately 0.4% (13 of 3,200 patients followed prospectively) in patients treated at doses of 300 to 450 mg/day. Additional data accumulated for the immediate release formulation of bupropion suggests that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, the disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

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, extreme caution should be used when treating patients with predisposing factors which increase the risk of seizures, including:

- Prior seizure (see 2 Contraindications).
- History of head trauma.
- Central nervous system (CNS) tumour.
- The presence of severe hepatic impairment.
- Excessive use of alcohol; addiction to opiates, cocaine, or stimulants.
- Use of concomitant medications that lower seizure threshold, including but not limited to antipsychotics, antidepressants, lithium, amantadine, theophylline, systemic steroids, quinolone antibiotics, and anti-malarials.
- Use of over-the-counter stimulants or anorectics.
- Diabetes treated with oral hypoglycemics or insulin.

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

In order to minimize the Risk of Seizure:

- The total daily dose of WELLBUTRIN SR must not exceed 300 mg (the maximum recommended dose)
- No single dose of WELLBUTRIN SR 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 WELLBUTRIN SR, they should contact their doctor or be taken to a hospital emergency ward immediately and should stop taking WELLBUTRIN SR. Treatment should not be restarted if a patient has experienced a seizure while taking WELLBUTRIN SR, WELLBUTRIN XL, CONTRAVE or ZYBAN.

- **Serotonin Toxicity / Serotonin Syndrome**

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with bupropion, including WELLBUTRIN SR, 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 WELLBUTRIN SR 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**

As with other antidepressants, WELLBUTRIN SR 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

- **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, 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 given an anti-depressant drug. This includes monitoring for agitation-type emotional and behavioural changes.

- **Clinical Worsening and Suicide**

The possibility of a suicide attempt in seriously depressed patients is inherent to the illness and may persist until significant remission occurs. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dosage changes, either increases or decreases. Close supervision of high-risk patients should accompany initial drug therapy, and consideration should be given to the need for hospitalization (see Potential association with behavioural and emotional changes, including self-harm).

It should be noted that a causal role for SSRIs and other newer anti-depressants in inducing self-harm or harm to others has not been established.

In order to reduce the risk of overdose, prescriptions for WELLBUTRIN SR (bupropion hydrochloride) should be written for the smallest number of tablets consistent with good patient management.

- **Agitation and Insomnia**

In placebo-controlled trials patients receiving WELLBUTRIN SR Tablets experienced an increased incidence of insomnia and anxiety relative to those receiving placebo (see 8 Adverse Reactions and Potential association with behavioural and emotional changes, including self-harm). These symptoms were sometimes of sufficient magnitude to require discontinuation of WELLBUTRIN SR, or concurrent treatment with sedative/hypnotic drugs. Insomnia may be minimized by avoiding bedtime doses and, if necessary, reduction in dose.

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

Patients treated with WELLBUTRIN SR 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 patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. WELLBUTRIN SR is expected to pose similar risks.

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**

Bupropion is extensively metabolized in the liver to active metabolites, which are largely further metabolised before being excreted by the kidneys. WELLBUTRIN SR treatment of patients with renal impairment should be initiated at a reduced dosage regimen, as 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.

Skin

- **Severe cutaneous adverse reactions (SCARs)**

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 WELLBUTRIN SR immediately if SCARs occur.

7.1 Special Populations

7.1.1 Pregnancy

There are no adequate and well-controlled studies of WELLBUTRIN SR in pregnant women. WELLBUTRIN SR should thus not be used during pregnancy unless the potential benefit is judged to outweigh the potential risk.

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 Exposure

Post-marketing reports indicate that some neonates exposed to SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants, such as WELLBUTRIN SR, 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 WELLBUTRIN SR during the third trimester, the physician should

carefully consider the potential risks and benefits of treatment (see 4 dosage and administration).

7.1.2 Breastfeeding

Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from WELLBUTRIN SR, 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): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of WELLBUTRIN SR in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (See 1.1 Pediatrics and Potential Association with Behavioural and Emotional Changes, Including Self Harm).

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Of the approximately 6000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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 10.3 Pharmacokinetics).

Bupropion is extensively metabolized in the liver to active metabolites, of which some are eliminated by the kidney, 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 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 Hepatic Impairment and Renal Impairment).

8 Adverse Reactions

8.1 Adverse Reaction Overview

The information included under Adverse Reactions is based on data from clinical trials with WELLBUTRIN SR (bupropion hydrochloride), the sustained release formulation of bupropion in the treatment of depression. Information on additional adverse events associated with the sustained release formulation of bupropion as well as the immediate release formulation of bupropion, is included in a separate subsection (see 8.5 Post-Market Adverse Reactions).

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials

Adverse events commonly encountered during the clinical development of WELLBUTRIN SR (incidence of 5% or greater; and higher incidence in WELLBUTRIN SR-treated, than placebo-treated patients) were

headache, constipation, dry mouth, nausea, dizziness, insomnia, tremor and tinnitus.

Adverse Events Associated with Discontinuation of Treatment

In placebo-controlled studies of depression (987 patients treated with WELLBUTRIN SR, and 385 treated with placebo), adverse events caused discontinuation in 7% of WELLBUTRIN SR-treated patients and 3% of placebo-treated patients. The more common events leading to discontinuation of WELLBUTRIN SR included nervous system disturbances (2.2%), primarily agitation, anxiety and insomnia; skin disorders (1.9%), primarily rashes, pruritus, and urticaria; general body complaints (1.0%), primarily headaches, and digestive system disturbances (1.0%), primarily nausea. Two patients in WELLBUTRIN SR treatment groups discontinued due to hallucinations (auditory or visual). The rates of premature discontinuation due to an adverse event were dose-related in these studies.

In an open label, uncontrolled (acute treatment and continuation) study of WELLBUTRIN SR, 11% patients (361 out of 3100) discontinued treatment due to an adverse event. Adverse events leading to premature discontinuation in 1% or more of patients were: headache (1.1%), nausea (1.0%), and insomnia (1.0%). Adverse events leading to premature discontinuation in 0.5% to 1% of patients were: anxiety (0.8%), rash (0.8%), agitation (0.7%), irritability (0.5%), and dizziness (0.5%). In those patients (n=1577) who went into the continuation phase after 8 weeks of treatment, 6 (0.4%) discontinued due to alopecia. Because this study was uncontrolled, it is not possible to reliably assess the causal relationship of these events to treatment with WELLBUTRIN SR.

8.2 Clinical Trial Adverse Reactions

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

Table 2 enumerates treatment-emergent adverse events that occurred at an incidence of 1% or more in placebo-controlled trials and were more frequent in the WELLBUTRIN SR group than the placebo group. Reported adverse events were classified using a COSTART-based Dictionary.

Table 2: Treatment Emergent Adverse Events Occurring in ≥1% of Patients in Placebo-Controlled Studies of Wellbutrin SR (pooled results from Studies 203, 205, and 212)

Body System	Adverse Experience	% AEs BUP SR 100-150 (n=382)	%AEs BUP SR 200-300 (n=491)	%AEs PBO (n=385)
Nervous System	Agitation	1.6	3.5	1.8
	Anxiety	4.5	4.3	3.1
	CNS stimulation	0	1.2	0.5
	Dizziness	7.1	8.6	5.5
	Hypertonia	1	1.2	0.5
	Insomnia	7.9	11.4	6.5
	Irritability	2.4	3.9	1.6
	Decreased libido	1	0.6	0.5
	Nervousness	4.5	4.1	2.6
	Somnolence	2.6	2.0	2.1
	Tremor	3.1	6.1	0.8
Respiratory	Pharyngitis	1.3	2.9	1.8
	Rhinitis	9.9	6.7	9.6

	Sinusitis	1.6	2.4	2.1
Skin	Pruritus	2.4	2.2	1.6
	Rash	2.1	4.1	1.3
	Sweating	2.4	5.1	1.6
	Urticaria	0.8	1.4	0
Special Senses	Amblyopia	2.9	2.4	1.8
	Taste perversion	1	1.4	0.3
	Tinnitus	3.9	5.1	1.8
Urogenital	Urinary Tract Infection	1	1.8	0.3
	Urinary frequency	1.3	2.4	1.6

8.3 Less Common Clinical Trial Adverse Reactions

In addition to the events noted above, the following adverse events (listed under section 8.5 Post-Market Adverse Reactions) have been reported in clinical trials and post-marketing experience with the sustained release formulation of bupropion in depressed patients and in non-depressed smokers, as well as in clinical trials and post-marketing experience with the immediate release formulation of bupropion.

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 = 1013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with WELLBUTRIN SR Tablets (n = 3100). All treatment-emergent adverse events are included except those listed in Table 2, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific 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 of major clinical importance are described in the Warnings and Precautions sections of the labelling.

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 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

8.5 Post-Market Adverse Reactions

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 sustained-release bupropion are included. The extent to which these events may be associated with WELLBUTRIN SR is unknown.

Body (General):

Infrequent were chills, facial edema, feeling jittery, musculoskeletal chest pain, and photosensitivity.

Rare was malaise.

Cardiovascular:

Infrequent were postural hypotension, stroke, and vasodilation.

Rare was syncope.

Also observed were Brugada syndrome, complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see Cardiovascular), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive:

Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, flatulence and thirst.

Rare was edema of tongue.

Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

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, and peripheral edema.

Very rare was hyponatremia.

Also observed was glycosuria.

Musculoskeletal:

Also observed were arthritis, muscle rigidity/fever/ rhabdomyolysis, muscle spasms and muscle weakness.

Nervous System:

Infrequent were abnormal coordination, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypesthesia, nightmare, suicidal ideation, taste is altered and vertigo.

Rare were amnesia, ataxia, derealization, and hypomania.

Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, serotonin syndrome and unmasking tardive dyskinesia.

Post-marketing reports suggest a causative association between dysphemia and WELLBUTRIN SR. Symptoms typically resolve upon discontinuation and may reappear with rechallenge. Exacerbation of pre-existing symptoms were also reported.

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

Psychiatric Disorders

Panic attack

Reproductive System and Breast Disorders

Dysmenorrhoea

Respiratory:

Rare was bronchospasm/dyspnea.

Also observed were blocked or stuffy nose, pneumonia and epistaxis.

Skin/Hypersensitivity:

Rare was maculopapular rash.

Very rare was acute generalized exanthematous pustulosis (AGEP).

Also observed were acne, alopecia, hirsutism, angioedema, exfoliative dermatitis, erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS), 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:

Infrequent were accommodation abnormality and dry eye.

Also observed were deafness, diplopia, and mydriasis.

Urogenital:

Infrequent were impotence, polyuria, and prostate disorder.

Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

Vascular Disorders

Hypertension

Hot flush

9 Drug Interactions

9.1 Serious Drug Interactions

- concomitant medicines that contain bupropion hydrochloride (e.g., WELLBUTRIN SR, ZYBAN, 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 the CYP2B6 isoenzyme (see 10.3 Pharmacokinetics). Therefore, the potential exists for a drug interaction between WELLBUTRIN SR and drugs that affect the CYP2B6 isoenzyme (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 WELLBUTRIN SR on the metabolism of other drugs.

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.

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In particular, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin, ritonavir, efavirenz).

9.3 Drug-Behaviour Interactions

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 or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions with WELLBUTRIN SR

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	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

		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.	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 should not be used in combination with tamoxifen and other treatment options should be considered (see Drugs Metabolized by Cytochrome P450 (CYP2D6))
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	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.

		(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).	
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 SR 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 WELLBUTRIN SR tablets with and without 800 mg of cimetidine. A single dose of cimetidine had no effect on single dose pharmacokinetic parameter estimates for bupropion, or hydroxybupropion, but caused a small statistically significant increase in the combined threohydro and 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 WELLBUTRIN SR to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.
Clopidogrel and Ticlopidine	CT	↑ plasma concentrations of bupropion and ↓ concentrations of hydroxybupropion The mean area	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

		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.	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 WELLBUTRIN SR 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.
Other Drugs with CNS Activity	T		The risk of using WELLBUTRIN SR in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of WELLBUTRIN SR and such drugs is required.

Transdermal Nicotine Interaction	CT		(see Cardiovascular)
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 WELLBUTRIN SR may be taken with or without food.

9.6 Drug-Herb Interactions

Interactions of WELLBUTRIN SR with herbal 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 result 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

WELLBUTRIN SR (bupropion hydrochloride is an antidepressant of the aminoketone class. It 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 the phenylethylamines.

The mechanism of bupropion's antidepressant activity is unknown but appears to be mediated by noradrenergic (and possibly dopaminergic), rather than serotonergic mechanisms. Preclinical studies have shown that bupropion blocks norepinephrine (NE) reuptake and dopamine (DA) reuptake. Its major metabolite (hydroxybupropion), which in man is present at blood levels 10-20-fold higher than bupropion, blocks only NA reuptake.

As with other antidepressants, bupropion and hydroxybupropion reduce firing rates of NE-neurons in the locus coeruleus. This effect is dependent on presynaptic stores of NE and can be blocked by α-adrenergic antagonists. The mild stimulating properties of bupropion appear to be due to its weak inhibition of dopamine (DA) uptake. This effect occurs at doses higher than those needed for antidepressant activity. The drug has no pharmacologically relevant effects on serotonin (5-HT).

The non-serotonergic mechanism of action of bupropion likely contributes to a distinct side effect profile that includes low rates of sexual dysfunction and somnolence (see 8.1 Adverse Reaction Overview).

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

Absorption

Bupropion has not been administered intravenously to humans; therefore, the absolute bioavailability of WELLBUTRIN SR 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 WELLBUTRIN SR to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. In two single-dose (150 mg) studies the mean peak concentration (C_{max}) values were 91 and 143 ng/mL. At steady state, the mean C_{max} following a 150 mg dose every 12 hours was 136 ng/mL.

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

Distribution

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200mcg/mL. The extent of protein binding of hydroxybupropion is similar to that of 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. In preclinical tests used to predict antidepressant activity, it has been observed that hydroxybupropion is comparable in potency to bupropion, while the other metabolites are one half to one tenth as potent. This may be of clinical

importance because the plasma concentrations of the metabolites are higher than those of bupropion.

In vitro results indicate that biotransformation of bupropion to hydroxybupropion is catalyzed primarily by CYP2B6, and to a much lesser extent by CYP1A2, 2A6, 2C9, 2E1 and 3A4 isozymes. Detectable levels of hydroxybupropion are not observed with CYP1A1 and CYP2D6 isozymes. Cytochrome P450 isoenzymes are not involved in the formation of threohyrobupropion. Following a single 150 mg dose of bupropion 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 of hydroxybupropion at steady state is about 17-fold higher than that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of hydroxybupropion, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by CYP2D6, there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see 9 Drug Interactions).

Elimination

In two single-dose (150 mg) studies the mean (±% CV) apparent clearance (Cl/F) of bupropion was 135 (±20%) and 209 L/hr (±21%). Following chronic dosing of 150 mg of WELLBUTRIN SR 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 of bupropion (estimated from a series of studies) is approximately 21 hours. Estimates of the half-lives of the metabolites determined from a multiple-dose study were 20 hours (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 ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and faeces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%. Bupropion and its metabolites exhibit linear kinetics following chronic administration of 150 to 300 mg/day.

Special Populations and Conditions

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

- **Pediatrics:** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of WELLBUTRIN SR in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.
- **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 and Geriatrics or Debilitated Patients).

- **Race:** The influence of race (Asian, Black and Caucasian) on the pharmacokinetics of bupropion (bupropion hydrochloride immediate release tablets) was evaluated based on dose normalized data pooled from five healthy volunteer studies. A comparison of pharmacokinetic parameter values did not detect any important differences in race with respect to AUC ($p = 0.5564$) and C_{max} ($p = 0.8184$).
- **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 liver 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 pharmacokinetic 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.

  In patients with hepatic impairment, treatment should be initiated at reduced dosage (see Hepatic/Biliary/Pancreatic and Hepatic Impairment).
- **Effect of Smoking:** In a single dose study, there were no significant differences in the pharmacokinetics of bupropion or its major metabolites in smokers compared with non-smokers.

11 Storage, Stability, and Disposal

Store at room temperature (15ºC – 25ºC).

Keep container tightly closed.

Keep out of sight and reach of children.

Part 2: Scientific Information

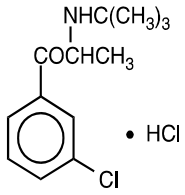
13 Pharmaceutical Information

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:	Bupropion hydrochloride has a maximum solubility in water of 312 mg/mL at 25ºC.

14 Clinical Trials

14.1 Clinical Trials by Indication

Major Depressive Illness

Table 4 - Summary of Patient Demographics for Clinical Trials in Major Depressive Illness

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Number of patients received Wellbutrin SR	Number of patients received Placebo
First study	Randomized, placebo-controlled, double-blind, parallel-group design with one-week placebo lead-in phase, followed by an 8-week treatment phase	Fixed Dose, Oral 150 mg/daily or 300 mg given as 150 mg twice daily Placebo	 121 120 121	1021	399
Second study	Randomized, placebo-controlled, double-blind, parallel-group design with one-week placebo lead-in phase, followed by an 8-week treatment phase	Fixed Dose, Oral 100 mg, 200 mg, 300 mg or 400 mg/day (given on a twice daily schedule) Placebo			

Third study	Randomized, placebo-controlled, double-blind, parallel-group design with one-week placebo lead-in phase, followed by an 8-week treatment phase	Flexible Dose[a] Oral 50-150 mg/day (given once daily) and 100-300 mg/day (twice daily schedule) Placebo	Approximately 150 patients per group		

[a] Patients began at the lowest dose in the range and were titrated to the highest tolerated dose in the range over a period of 7 days. Investigators had the option to titrate down when a higher dose was not well tolerated.

Table 5 - Results of Studies

Study 1	Study 2	Study 3
The response to treatment was evaluated at regular intervals using the Hamilton Rating Scale for Depression (HAMD), Clinical Global Impressions Scales of Severity (CGI-S) and Improvement (CGI-I) Scale. Both the observed and the last observation carried forward (LOCF) values were analysed.		
The HAMD, CGI-S (change from baseline) and CGI-I scores for both WELLBUTRIN SR groups at endpoint were statistically significantly superior to placebo. Both active treatment groups showed a similar magnitude of improvement during the trial.	The magnitude of the mean change scores was consistently greater for all active groups than placebo by day 21. At endpoint, scores in the 100 mg group were statistically significantly superior to placebo on all rating scales, while the higher dose groups followed a similar pattern but did not achieve statistical significance.	The mean daily dose calculated from day 8 onwards was 144 mg in the 50-150 mg arm and 276 mg in the 100-300 mg arm, indicating that the vast majority of patients remained on the highest allowable dose in their respective groups for the duration of the study. Efficacy measures at endpoint for the 50-150 mg/day group were statistically significantly superior to placebo. The higher dose group followed a similar pattern but did not achieve statistical significance at endpoint. A combined endpoint analysis of all patients treated with WELLBUTRIN SR in the trial, demonstrated statistically significant superiority on all efficacy measures compared to placebo.

Patients receiving WELLBUTRIN SR at doses of 100 mg to 150 mg/day in single or divided doses experienced improvement relative to placebo on the major indices of depression. Clinical response did not improve with increasing dose, indicating a flat dose-response relationship in the range of doses studied.

16 Non-Clinical Toxicology

General Toxicology

Three acute toxicity studies (LD_{50}) were carried out in mice and rats at doses ranging from 175 to 700 mg/kg. The LD_{50} ranged from 263 mg/kg in male Long-Evans rats to 636 mg/kg in female CD-1 mice. Clinical signs included convulsions, ataxia, loss of righting reflex, laboured breathing, prostration, salivation and ptosis.

Five repeated dose toxicity studies have been performed in the rat. 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, 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 150 mg/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.

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.

Increase in liver weights with associated hypertrophy in rats and dogs are commonly observed in lifetime bioassays with high doses of drugs which are inducers of microsomal enzymes. Such enzyme induction has been noted in animals but not in humans receiving bupropion. Moreover, available human data do not indicate liver toxicity associated with bupropion immediate release or sustained release.

Carcinogenicity

Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day bupropion, 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; 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 tumours of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2 to 3 times control mutation rate) in 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. The relevance of these results in estimating the risk to human exposure to therapeutic doses is unknown.

Reproductive and Developmental Toxicology

A two-generation reproductive and fertility study in Long Evans rats receiving 100, 200, 300 mg/kg bupropion daily by gavage revealed no treatment or compound related effects observed on mating or fertility performance. No compound related effects were observed in reproductive ability, fertility, gross anatomic abnormalities, foetal deaths or pup survival and growth during lactation. In F1 generation females no compound related effects were observed on lactation, body weight at sacrifice, reproduction performance and post-mortem findings. Similarly, no compound related findings were observed in the

clinical condition, reproductive performance or necropsy of the F1 males. In the F2 generation, no compound related effects were observed on the male: female ratio of pups, survival or bodyweight. No compound related effects were observed on necropsy.

Teratology studies have been performed at doses up to 450 mg/kg in rats, and at doses up to 150 mg/kg in rabbits (approximately 7 to 11 and 7 times the MRHD, respectively, on a mg/m^2 basis), and have revealed no evidence of harm to the fetus due to bupropion.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr WELLBUTRIN® SR

Bupropion Hydrochloride Sustained-Release Tablets

This patient medication information is written for the person who will be taking **WELLBUTRIN SR**. 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 **WELLBUTRIN SR**, talk to a healthcare professional.

Serious warnings and precautions box

New or worsened emotional or behavioural problems:

- When you first start taking WELLBUTRIN SR or when your dose is adjusted, you may feel worse instead of better. This can include 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 depressed. Ask them to read this leaflet. You might ask them to tell you if they:
  - think your depression is getting worse, or
  - are worried about changes in your behaviour.
- If your depression worsens or you experience changes in your behaviour, tell your healthcare professional right away. Do not stop taking your medicine as it takes time for WELLBUTRIN SR to work.

Self-harm or suicide

- Antidepressants, such as WELLBUTRIN SR, 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 WELLBUTRIN SR is used for:

WELLBUTRIN SR is used in adults to relieve the symptoms of:

- **Depression** (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain)

How WELLBUTRIN SR Works:

WELLBUTRIN SR belongs to a group of medicines called antidepressants. WELLBUTRIN SR is thought to

block reuptake of chemicals in the brain called noradrenaline and dopamine. This helps to relieve your symptoms of depression.

The ingredients in WELLBUTRIN SR are:

Medicinal ingredient: Bupropion Hydrochloride.

Non-medicinal ingredients: Carnauba Wax, Cysteine Hydrochloride, Edible Black Ink, FD&C Blue No. 2 Lake, FD&C Red No. 40 Lake, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80 and Titanium Dioxide.

WELLBUTRIN SR comes in the following dosage forms:

Sustained-release tablets: 150 mg.

Do not use WELLBUTRIN SR if:

- you are allergic to bupropion or any of the other ingredients in WELLBUTRIN SR tablets.
- you are taking any other medicines which contain bupropion hydrochloride, such as WELLBUTRIN XL, ZYBAN® and CONTRAVE®.
- you have been diagnosed with epilepsy or have a history of seizures or fits.
- you previously had seizures while taking the antidepressants WELLBUTRIN® XL, the smoking cessation medication ZYBAN® or the weight-loss medication CONTRAVE®.
- you have or have had an eating disorder, such as:
    - bulimia (binge eating and throwing up 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 monoamine oxidase inhibitor (MAOI) antidepressants, such as phenelzine, moclobemide, and tranylcypromine.
- 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 WELLBUTRIN SR. 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, ZYBAN® 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 WELLBUTRIN SR.
- 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 WELLBUTRIN SR may cause your speech disorder to come back or worsen.

Other warnings you should know about:

WELLBUTRIN SR can cause serious side effects, including:

- **Seizures** (fits): Your risk of seizures increases when you take WELLBUTRIN SR, especially:
  - if your dose of WELLBUTRIN SR increases;
  - if you do not take WELLBUTRIN SR as prescribed;
  - if you take certain medicines at the same time;
  - if you are already at higher than usual risk of seizures.

- **Angle-closure glaucoma** (eye pain caused by increased pressure in the eyes): WELLBUTRIN SR can cause an acute attack of glaucoma. Having your eyes examined before you take WELLBUTRIN SR

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.

- **Liver disorders:** This includes hepatitis (inflammation of the liver) and jaundice (yellowing of the skin and eyes).

- **Hallucinations, delusions, paranoia** (sensing or believing things that are not there).

- **Mania**: Antidepressants, such as WELLBUTRIN SR, may trigger manic episodes in patients with bipolar disorder during the depressed state of their illness or psychosis in other susceptible patients.

- **Hypertension** (high blood pressure): Your healthcare professional may monitor your blood pressure, especially if you are using nicotine patches while you are taking WELLBUTRIN SR.

- **Hyponatremia** (low sodium in the blood).

- **Serotonin toxicity (also known as serotonin syndrome):** WELLBUTRIN SR 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 WELLBUTRIN SR with certain anti-depressants or migraine medications.

  Serotonin toxicity symptoms include:

  - fever, sweating, shivering, diarrhea, nausea, vomiting
  - muscles shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination, flushing
  - fast heartbeat, changes in blood pressure
  - confusion, agitation, restlessness, hallucinations, mood changes unconsciousness, anxiety and coma

- **Severe allergic reactions:**
  - WELLBUTRIN SR 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 WELLBUTRIN SR, your symptoms may not go away even after you stop taking it.

- **Severe skin reactions:** Taking WELLBUTRIN SR may cause serious skin reactions. These include 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 WELLBUTRIN SR and contact your healthcare professional immediately if you experience these symptoms.

- **Systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE):** WELLBUTRIN SR 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.
- **Brugada syndrome** (serious heart problem): WELLBUTRIN SR 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 WELLBUTRIN SR.

  Before you start taking WELLBUTRIN SR, 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 for more information on these and other serious side effects.

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

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

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

Driving and using machines:

- WELLBUTRIN SR may impair your ability to do tasks requiring judgement, thinking or motor skills.
- You should not drive or use machines until you know how WELLBUTRIN SR affects you.

Pregnancy:

- If you are pregnant, your healthcare professional will determine if WELLBUTRIN SR is right for you. They will also discuss the risks of birth defects and complications after birth if you take WELLBUTRIN SR during pregnancy.
- If you have been prescribed WELLBUTRIN SR 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 WELLBUTRIN SR. It is very important that you do **not** stop taking WELLBUTRIN SR without first consulting with your healthcare professional.

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

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 WELLBUTRIN SR include:

- medicines that contain bupropion hydrochloride (e.g., WELLBUTRIN XL, ZYBAN® 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 WELLBUTRIN SR if you are taking any of these medicines. Ask your healthcare professional if you are unsure

The following may also interact with WELLBUTRIN SR:

- Medicines used to treat depression and other mental illnesses, such as citalopram, paroxetine, venlafaxine, nortriptyline, imipramine, desipramine, fluoxetine, sertraline, phenelzine, 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 medicines 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 WELLBUTRIN SR:

- WELLBUTRIN SR sustained-release tablets should not be confused with other bupropion formulations.
- To minimize your risk of seizures:

- Take WELLBUTRIN SR exactly as directed by your healthcare professional. If you have any problems with your dosing routine, contact your healthcare professional.
- **Never** take more than 150 mg of WELLBUTRIN SR at one time.
- **Never** increase the dose of WELLBUTRIN SR unless your healthcare professionaltells you to.
- If you are prescribed 300 mg a day, take your WELLBUTRIN SR doses at least 8 hours apart, at about the same times each day. If you have trouble sleeping whiletaking WELLBUTRIN SR, take the second tablet earlier in the evening (but at least 8 hours after the first tablet).

- WELLBUTRIN SR tablets must be taken orally. Swallow your WELLBUTRIN SR tablets whole, with water. Do **not** crush, cut or chew tablets.
- WELLBUTRIN SR can be taken with or without food.
- The effects of your medicine may not be noticeable in the first few days of treatment and improvement may take several weeks. If you are concerned that your medicine is not working:
  - continue taking your medicine as it takes time for WELLBUTRIN SR to work, and
  - discuss this with your healthcare professional.
- You should talk to your healthcare professional before you stop taking your medicationon your own. You may experience unwanted side effects if you suddenly stop taking WELLBUTRIN SR.

Usual dose:

- The usual adult dose is one 150 mg tablet **once** daily.
- Your dose may be increased to one 150 mg tablet **twice** daily (i.e. 300 mg per day) after 1 week. Be sure to take your doses at least 8 hours apart.

Overdose:

The symptoms of an overdose include:

- Drowsiness
- Fainting
- Respiratory arrest (breathing stops)
- Amnesia (loss of memories)
- Seizures
- Irregular heartbeat, which may be life-threatening.
- Serotonin syndrome, which is a serious condition and may 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 WELLBUTRIN SR 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 WELLBUTRIN SR, 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 WELLBUTRIN SR:

These are not all the possible side effects you may have when taking WELLBUTRIN SR. If you experience any side effects not listed here, tell your healthcare professional.

The side effects of WELLBUTRIN SR may include:

- **Very common side effects** (may affect more than 1 in 10 people)
  - constipation,
  - dry mouth,
  - headache,
  - insomnia (a sleeping disorder that makes it hard to fall asleep),
  - nausea,
  - dizziness,

- **Common side effects** (may affect up to 1 in 10 people)
  - abnormal dreams,
  - acne,
  - blocked or stuffy nose,
  - decreased weight,
  - feeling jittery,
  - flatulence,
  - hot flush,
  - memory loss,
  - muscle spasms,
  - painful periods or menstrual cramps,
  - panic attack,
  - ringing in ears,
  - shakiness,
  - taste is altered,
  - thirsty,
  - tremor,

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the/this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
Rare			
Seizures (fits): loss of consciousness with uncontrollable shaking			√
Systemic lupus erythematosus (SLE) and **cutaneous lupus erythematosus (CLE)**: red blotchy rash mainly on the facewhich may be accompanied by fatigue, pain or swelling in joints, muscle pain, fever, nausea, loss of appetite		√	
Very rare			
Agression		√	
Angle-closure glaucoma (eye pain caused by increased pressure in the eye): blurred vision, halos around lights, eye pain and redness, nausea and vomiting, severe headache			√
Hallucinations, delusions, paranoia (sensing or believing things that are not there)		√	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swellingin your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations	√		
Hyponatremia (low blood sodium): lethargy, confusion, muscular twitching, achy, stiffor uncoordinated muscles, seizure or coma		√	
Inability to urinate		√	
Liver Disorders-(including hepatitis and jaundice): yellowing of the skin or eyes,		√	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the/this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite, itching			
Mania: elevated or irritable mood, talking fast, taking more risks, needing less sleep, or racing thoughts		√	
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		√	
Thoughts of death or suicide: thoughts or actions about hurting or killing yourself or other people			√
Poor blood sugar control	√		
Serotonin toxicity (also known as serotonin syndrome): feeling of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (above 38°C), rigid muscles			√
Severe allergic reactions: red and lumpy or blistering skin rash, swelling of the face or throat, trouble breathing, collapse, blackout, severe muscle or joint pain, chest pain or fever			√
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			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the/this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
urine, shortness of breath, chest pain or discomfort, feeling thirsty, urinating less often, less urine.			
Unknown			
Brugada syndrome (serious heart problem): dizziness, fainting, fast heartbeat, palpitations, abnormal heartbeat, seizures (fits), or 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 WELLBUTRIN SR at room temperature (15ºC to 25ºC).
- Keep container tightly closed.
- If your healthcare professional tells you to stop taking WELLBUTRIN SR, please return any leftover medicine to your pharmacist.
- Keep out of reach and sight of children.

If you want more information about WELLBUTRIN SR:

- 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) or by calling 1-800-361-4261.

This leaflet was prepared by Bausch Health, Canada Inc.

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