PRODUCT MONOGRAPH

PrTEVA-BUPROPION XL

Bupropion Hydrochloride Extended-Release Tablets

Manufacturer's Standard

150 mg and 300 mg

Antidepressant

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Date of Revision:
May 5, 2021

Submission Control No: 251769

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Extended-Release Tablets: 150 mg and 300 mg	Hydroxypropyl Cellulose, Silicified Microcrystalline Cellulose, Stearic Acid **The tablet film coating contains:** Ethylcellulose, Hydroxypropyl Cellulose, Methacrylic Acid Copolymer, Talc, Titanium Dioxide, Triethyl Citrate **The tablet imprinting contains:** Hypromellose, Iron Oxide Black, Isopropyl Alcohol, Propylene Glycol

INDICATIONS AND CLINICAL USE

Adults

Major Depressive Disorder:
TEVA-BUPROPION XL is indicated for the symptomatic relief of major depressive illness.

The efficacy of bupropion hydrochloride extended release tablets for the treatment of major depressive episode was established in three, double-blind, 8 week, placebo-controlled trials, in adult outpatients with a history of major depressive illness. The effectiveness of bupropion hydrochloride extended-release tablets in long-term use (greater than 8 weeks) has not been evaluated in controlled trials. Therefore, the physician who elects to use TEVA-BUPROPION XL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Prevention Of Seasonal Major Depressive Episodes
TEVA-BUPROPION XL is indicated for the prevention of major depressive illness with an autumn-winter seasonal pattern.

The efficacy of bupropion hydrochloride extended-release tablets for the prevention of seasonal major depressive episodes was established in three double-blind, placebo-controlled trials in adult outpatients with a history of major depressive disorder with an autumnal-winter seasonal pattern as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria. Treatment duration was approximately 4 to 6 months.

The efficacy of bupropion hydrochloride extended-release tablets in preventing seasonal depressive episodes has not been compared to light therapy.

Pediatrics (<18 years of age)
TEVA-BUPROPION XL is not indicated for use in patients below the age of 18 years (see WARNINGS AND PRECAUTIONS, General, Potential Association With Behavioural and Emotional Changes, Including Self-Harm).

CONTRAINDICATIONS

To reduce the risk of seizures, TEVA-BUPROPION XL (bupropion hydrochloride) is contraindicated in patients:

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

To reduce risks due to drug interaction, the concomitant use of TEVA-BUPROPION XL is contraindicated in patients currently taking:

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

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

- TEVA-BUPROPION XL is contraindicated in patients with known hypersensitivity to bupropion or any of the components of the formulation.

WARNINGS AND PRECAUTIONS

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 antidepressants, 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 behavior is advised in patients of all ages given an anti-depressant drug. This includes monitoring for agitation-type emotional and behavioural changes.

Seizures:

Patients should be made aware that TEVA-BUPROPION XL contains bupropion hydrochloride. TEVA-BUPROPION XL should NOT be administered to patients already receiving a product containing bupropion hydrochloride (see CONTRAINDICATIONS).

The recommended dose of extended release bupropion tablets should not be exceeded, since bupropion is associated with a dose-related risk of seizure. The overall incidence of seizure with bupropion hydrochloride extended-release tablets in clinical trials at doses up to 450 mg/day was approximately 0.1% (2 of 2146 subjects/patients). Seizure incidence in clinical trials with doses of 450 mg/day was approximately 0.39% (2 of 537 subjects). There were no seizures in clinical trials where subjects (n=1638) were treated up to the maximum recommended dose of 300 mg/day. In post marketing data however, seizures have been observed across all doses and formulations of bupropion hydrochloride.

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 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 TEVA-BUPROPION XL must not exceed 300 mg (the maximum recommended dose).

If a Seizure Occurs:
Patients should be warned that if they experience a seizure while taking TEVA-BUPROPION XL, they should contact their doctor or be taken to a hospital emergency ward immediately, and should stop taking TEVA-BUPROPION XL. Treatment should not be restarted if a patient has experienced a seizure while taking a formulation containing bupropion hydrochloride.

Misuse of Bupropion hydrochloride extended release tablets by injection or inhalation

TEVA-BUPROPION XL is intended for oral use only. The inhalation of crushed tablets or injection of dissolved bupropion has been reported, and may lead to a rapid release, faster absorption and a potential overdose. Seizures and/or cases of death have been reported when bupropion has been administered intra-nasally or by parenteral injection.

Potential for 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.

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 WARNINGS AND PRECAUTIONS: 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 TEVA-BUPROPION XL (bupropion hydrochloride) should be written for the smallest number of tablets consistent with good patient management.

Allergic Reactions:

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 postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. In uncontrolled and controlled clinical trials, skin disorders, primarily rashes, pruritis, and urticaria, lead to discontinuation of 1.5% and 1.9 %, respectively of bupropion-treated subjects. A patient should stop taking TEVA-BUPROPION XL 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.

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 Interaction).

Agitation and Insomnia:

In placebo controlled trials patients receiving bupropion hydrochloride sustained release Tablets experienced an increased incidence of insomnia and anxiety relative to those receiving placebo (see ADVERSE REACTIONS and WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM). These

symptoms were sometimes of sufficient magnitude to require discontinuation of bupropion hydrochloride sustained-release tablets, 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 bupropion hydrochloride sustained-release tablets 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 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. TEVA-BUPROPION XL is expected to pose similar risks.

Altered Appetite and Weight:

In clinical trials bupropion hydrochloride sustained-release tablets 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 bupropion hydrochloride sustained-release tablets 100 mg/day, 1.4 kg at 150 mg/ day, and 2.3 kg at 300 mg/day.

In 3 placebo-controlled clinical trials of seasonal depression using bupropion hydrochloride extended-release tablets (up to 6 months of treatment), 23% of subjects who received bupropion hydrochloride extended-release tablets lost >5lbs, compared to 11% of subjects who received placebo. The mean weight change from baseline to the subject's last visit was -0.9 kg in the bupropion hydrochloride extended-release tablets group and 0.8 kg in the placebo group.

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.

Cardiovascular Effects:

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 preexisting hypertension.

Data from a comparative study of the sustained-release formulation of bupropion, 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 preexisting hypertension. Three patients (1.2%) treated with the combination of bupropion hydrochloride sustained-release tablets 150 mg 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 bupropion hydrochloride sustained-release tablets 150 mg 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.

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 Drug Interactions).

Angle-Closure Glaucoma

As with other antidepressants, bupropion hydrochloride extended release tablets 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.

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, TEVA-BUPROPION XL 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 DOSAGE AND ADMINISTRATION; ACTIONS AND CLINICAL PHARMACOLOGY).

Hyponatremia

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

Renal Impairment:

Bupropion is extensively metabolized in the liver to active metabolites, which are largely further metabolized before being excreted by the kidneys. TEVA-BUPROPION XL 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 (eg., insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels.

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

Serotonin Syndrome:
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 TEVA-BUPROPION XL 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 (see also OVERDOSAGE).

Special Populations

Pregnancy, Labour and Delivery:

There are no adequate and well-controlled studies of bupropion hydrochloride extended-release tablets in pregnant women. TEVA-BUPROPION XL 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 (eg, ventricular and atrial septal defects) with maternal exposure to bupropion in the first trimester. Bupropion should be initiated during pregnancy or in women who intend to become pregnant only if benefits outweigh the potential risk to the fetus.

Third Trimester Exposure
Post-marketing reports indicate that some neonates exposed to SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants, such as bupropion hydrochloride

sustained-release tablets, 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 TEVA-BUPROPION XL during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. (See DOSAGE AND ADMINISTRATION).

Lactation:

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 bupropion hydrochloride extended-release tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age):

TEVA-BUPROPION XL is not indicated for use in patients below the age of 18 years (See WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self Harm. See also INDICATIONS, Pediatrics; DOSAGE AND ADMINISTRATION, Special Patient Populations-Children).

Geriatrics:

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

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another single and multiple dose pharmacokinetic study, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see ACTION AND CLINICAL PHARMACOLOGY, 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 elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see WARNINGS AND PRECAUTIONS, Hepatic or Renal Impairment).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The information included under ADVERSE REACTIONS is based on data from clinical trials with bupropion hydrochloride extended-release tablets, the once daily extended release formulation of bupropion in the treatment of major depressive disorder (MDD) and prevention of seasonal major depressive episodes. 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 Events Observed During Development and Post-Marketing Experience of Bupropion with other formulations or indications).

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials

Major Depressive Disorder

The most common adverse events encountered in bupropion hydrochloride extended-release tablets MDD clinical trials (incidence of ≥5% and higher incidence in bupropion hydrochloride extended-release tablets treated than placebo treated) were, dry mouth, nausea, constipation, insomnia, dizziness, anxiety, decreased appetite.

Prevention Of Seasonal Major Depressive Episodes

The most common adverse events encountered in bupropion hydrochloride extended-release tablets seasonal depression clinical trials (incidence of ≥5% and higher incidence with bupropion hydrochloride extended-release tablets than placebo) were, dry mouth, nausea, constipation, flatulence, headache, dizziness, insomnia, anxiety, nasopharyngitis, upper respiratory infection, and sinusitis.

Adverse Events Associated with Discontinuation of Treatment

Major Depressive Disorder

In placebo controlled studies in depression (411 patients treated with bupropion hydrochloride extended-release tablets, and 412 treated with placebo), adverse events caused discontinuation in 6% of bupropion hydrochloride extened-release tablets treated patients and 3% of placebo-treated patients. All adverse events leading to discontinuation of bupropion hydrochloride extended-release tablets occurred with an incidence of less than 1%.

Prevention of Seasonal Major Depression

In placebo-controlled clinical trials, 9% of patients treated with bupropion hydrochloride extended-release tablets and 5% of patients treated with placebo discontinued treatment due to adverse events. The adverse events in these trials that led to discontinuation in at least 1% of patients treated with bupropion hydrochloride extended-release tablets and at a rate numerically greater than the placebo rate were insomnia (2% vs <1%) and headache (1% vs <1%).

Prospective Studies in Major Depressive Disorder Trials To Assess Drug-related Adverse Events on Sexual Function

Using identical protocols, studies AK130926 and AK130927 set orgasm dysfunction as a primary outcome measure, in addition to the HAMD-17 score. The studies compared the effects of bupropion hydrochloride extended-release tablets, placebo and a representative SSRI as a positive control, in a sample of depressed subjects with normal orgasmic function at baseline. Orgasm dysfunction, as defined by presence of orgasm delay, orgasm failure, or both, was based on investigator interview at the 0, 2, 4, 6 and 8 week points in the study.

In each of the two studies, AK130926 and AK130927, the percentage of subjects with orgasm dysfunction in the bupropion hydrochloride extended-release tablets groups (16% and 13%) were not significantly different from the placebo groups (8% and 11%). Statistically, these observed rates in both the placebo groups and the bupropion hydrochloride extended-release tablets groups were significantly lower as compared to the SSRI positive control groups (29% and 32%).

Clinical Trial Adverse Drug Reactions

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

Major Depressive Disorder (MDD)

Table 1 enumerates treatment-emergent adverse events that occurred at an incidence of 1% or more in placebo-controlled trials, and were more frequent in the bupropion hydrochloride extended-release tablets group than the placebo group. Reported adverse events were classified using MedDRA. (Treatment-Emergent adverse events related to sexual function were assessed using specific outcome measures in two placebo-controlled studies – see ADVERSE EVENTS, PROSPECTIVE STUDIES TO ASSESS DRUG-RELATED ADVERSE EVENTS ON SEXUAL FUNCTION).

Table 1: Adverse Events in MDD Placebo-Controlled Studies
Treatment – Emergent Adverse Experiences Occurring in ≥1% of Patients taking Bupropion Hydrochloride Extended-Release Tablets (with an incidence greater than placebo)

System Organ Class	Preferred Term	Pooled Results	
		Placebo n=412	Bupropion Hydrochloride Extended-Release Tablets n=411

System Organ Class	Preferred Term	Pooled Results	
		Placebo n=412	Bupropion Hydrochloride Extended-Release Tablets n=411
Cardiac Disorders	Palpitations	10 (2%)	13 (3%)
Ear and Labyrinth Disorders	Tinnitus	3 (<1%)	11 (3%)
Eye Disorders	Vision Blurred	4 (<1%)	8 (2%)
Gastrointestinal Disorders	Nausea	42 (10%)	63 (15%)
	Dry Mouth	38 (9%)	79 (19%)
	Constipation	27 (7%)	41 (10%)
	Abdominal Upper Pain	7 (2%)	17 (4%)
	Vomiting	8 (2%)	10 (2%)
	Abdominal Pain	5 (1%)	6 (1%)
General Disorders	Feeling Jittery	6 (1%)	9 (2%)
	Pyrexia	4 (<1%)	5 (1%)
	Chest Pain	2 (<1%)	5 (1%)
	Chest Discomfort	0	5 (1%)
Infections & Infestations	Nasopharyngitis	11 (3%)	16 (4%)
	Influenza	6 (1%)	8 (2%)
Investigations	Weight decreased	1 (<1%)	8 (2%)
	Heart Rate Increased	0	6 (1%)
Metabolism and Nutrition	Decreased appetite	14 (3%)	19 (5%)
Musculoskeletal Disorders	Myalgia	7 (2%)	10 (2%)
Nervous System Disorders	Dizziness	15 (4%)	32 (8%)
	Tremor	4 (<1%)	17 (4%)
	Dysgeusia	2 (<1%)	12 (3%)
Psychiatric Disorders	Insomnia	17 (4%)	40 (10%)
	Irritability	16 (4%)	17 (4%)

System Organ Class	Preferred Term	Pooled Results	
		Placebo n=412	Bupropion Hydrochloride Extended-Release Tablets n=411
	Anxiety	8 (2%)	21 (5%)
	Restlessness	8 (2%)	11 (3%)
	Initial Insomnia	4 (<1%)	5 (1%)
	Middle insomnia	3 (<1%)	5 (1%)
	Panic Attack	1 (<1%)	5 (1%)
Respiratory Disorders	Cough	6 (1%)	10 (2%)
Skin & Subcutaneous Tissue	Hyperhidrosis	5 (1%)	9 (2%)
	Rash	5 (1%)	11 (3%)
	Pruritus	5 (1%)	6 (1%)
Vascular Disorders	Hot Flush	2 (<1%)	5 (1%)
	Hypertension	3 (<1%)	5 (1%)

Prevention of Seasonal Major Depression

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 bupropion hydrochloride extended-release tablets group than the placebo group.

Table 2: Adverse Events Seasonal Depression Placebo-Controlled Studies
Treatment – Emergent Adverse Experiences Occurring in ≥1% of Patients taking Bupropion Hydrochloride Extended-Release Tablets
(with an incidence greater than placebo)

System Organ Class	Preferred Term	Pooled Results	
		Placebo n=511	Bupropion Hydrochloride Extended-Release Tablets n=537
Gastrointestinal Disorders	Dry mouth	79 (15%)	137 (26%)
	Nausea	39 (8%)	68 (13%)

System Organ Class	Preferred Term	Pooled Results	
		Placebo n=511	Bupropion Hydrochloride Extended-Release Tablets n=537
	Constipation	10 (2%)	47 (9%)
	Flatulence	17 (3%)	30 (6%)
	Abdominal pain	2 (<1%)	11 (2%)
	Toothache	5 (<1%)	8 (1%)
Vascular Disorders	Hypertension	0	10 (2%)
	Hot flush	1 (<1%)	7 (1%)
Metabolism and Nutrition	Decreased appetite	6 (1%)	20 (4%)
Respiratory Disorders	Cough	16 (3%)	21 (4%)
	Dyspnoea	2 (<1%)	8 (1%)
Nervous System Disorders	Headache	138 (27%)	182 (34%)
	Dizziness	23 (5%)	31 (6%)
	Tremor	6 (1%)	18 (3%)
	Dysgeusia	3 (<1%)	8 (1%)
	Memory impairment	0	6 (1%)
General Disorders	Feeling Jittery	8 (2%)	17 (3%)
	Thirst	3 (<1%)	6 (1%)
	Chest pain	2 (<1%)	6 (1%)
Psychiatric Disorders	Insomnia	58 (11%)	84 (16%)
	Anxiety	22 (4%)	28 (5%)
	Middle insomnia	7 (1%)	12 (2%)
	Abnormal dreams	5 (<1%)	11 (2%)
	Agitation	4 (<1%)	11 (2%)
	Initial insomnia	3 (<1%)	11 (2%)
	Disturbance in attention	4 (<1%)	7 (1%)

System Organ Class	Preferred Term	Pooled Results	
		Placebo n=511	Bupropion Hydrochloride Extended-Release Tablets n=537
Infections & Infestations	Nasopharyngitis	62 (12%)	71 (13%)
	Upper respiratory tract infection	43 (8%)	47 (9%)
	Sinusitis	20 (4%)	27 (5%)
	Urinary tract infection	5 (<1%)	8 (1%)
	Pharyngitis streptococcal	3 (<1%)	6 (1%)
Skin & Subcutaneous Tissue	Rash	11 (2%)	14 (3%)
	Acne	1 (<1%)	8 (1%)
	Pruritis	4 (<1%)	7 (1%)
	Urticaria	0	7 (1%)
Musculoskeletal Disorders	Myalgia	11 (2%)	14 (3%)
	Pain in extremity	10 (2%)	14 (3%)
	Muscle cramp	1 (<1%)	7 (1%)
Ear and Labyrinth Disorders	Tinnitus	3 (<1%)	18 (3%)
Reproductive Disorders	Dysmenorrhoea	2 (<1%)	11 (2%)
Eye Disorders	Vision Blurred	3 (<1%)	7 (1%)

Less Common Bupropion Hydrochloride Extended-Release Tablets Clinical Trial Adverse Drug Reactions (<1%)

The following treatment-emergent adverse drug reactions were reported with <1% incidence in the three pooled MDD, and the three pooled seasonal depression bupropion hydrochloride extended-release tablets clinical trials. The extent to which these events may be associated with bupropion hydrochloride extended-release tablets is unknown.

Blood and Lymphatic System Disorders: Lymphadenopathy, anaemia.

Cardiovascular Disorders: Cardiac flutter, tachycardia, supraventricular tachycardia.

Ear and Labyrinth Disorders: Ear pain, motion sickness, vertigo, hyperacusis.

Eye Disorders: Eye pruritis, conjunctivitis, eye pain, keratoconjunctivitis sicca, acquired dacryostenosis, lacrimation decreased, lacrimation increased, photophobia, vitreous floaters.

Gastrointestinal Disorders: Loose stools, stomach discomfort, gastroesophageal reflux disease, frequent bowel movements, gastrointestinal discomfort, lower abdominal pain, eructation, gastritis, halitosis, gastric irritation, hyperacidity, oral hypoaesthesia, lip dry, pancreatitis, abdominal distension, food poisoning, defaecation urgency, duodenal ulcer haemorrhage, gastrointestinal pain, gingival pain, gingivitis, infrequent bowel movements, mouth ulceration, oral pain.

General Disorders and Administration Site Conditions: Pain, oedema peripheral, asthenia, feeling abnormal, feeling hot, influenza like illness, thirst, energy increased, hunger, malaise, rigors, respiratory sighs, energy increased, feeling cold, impaired healing, injection site joint pain, temperature tolerance.

Immune System Disorders: seasonal allergy**,** drug hypersensitivity, latex allergy, hypersensitivity, food allergy.

Infections and Infestations: bronchitis, fungal infection, ear infection, gastroenteritis, bacterial vaginitis, cystitis, herpes zoster, pharyngitis, vaginal mycosis, wound infection, infective conjunctivitis, dental caries, herpes virus infection, hordeolum, localized infection, viral upper respiratory tract infection, respiratory tract infection, rhinitis, tooth infection, laryngitis, tooth abscess, pneumonia, folliculitis, viral gastritis, hepatitis C, prostate infection, tinea pedis, tonsillitis.

Injury, poisoning and procedural complications: contusion, joint sprain, muscle strain, skin laceration, excoriation, post procedural pain, limb injury, sunburn, accidental overdose, arthropod bite, facial bones fracture, mouth injury, soft tissue injury, wrist fracture, back injury, joint injury, epicondylitis, concussion, fall, animal scratch, laceration, lower limb fracture.

Investigations: Blood pressure increased, weight increased, heart rate irregular.

Metabolism and Nutrition Disorders: Anorexia, food craving, increased appetite, dehydration, hypercholesterolaemia.

Musculoskeletal and Connective Tissue Disorders: muscle tightness, neck pain, muscle twitching, pain in jaw, musculoskeletal stiffness, muscle spasms, sensation of heaviness, tendonitis, chest wall pain, musculoskeletal pain, bursitis, flank pain, joint stiffness, joint swelling, muscular weakness, musculoskeletal chest pain, osteoporosis, tendon disorder.

Neoplasms, (benign, malignant incl. Cysts and polyps): basal cell carcinoma, cyst, breast cancer.

Nervous System Disorders: Amnesia, depressed level of consciousness, disturbance in attention, dyslexia, sinus headache, hypersomnia, hypoaesthesia, lethargy, migraine, muscle contractions involuntary, myoclonus, paraesthesia, oral paraesthesia, parosmia, sedation, tension headache, psychomotor hyperactivity, somnolence, carpel tunnel syndrome, nerve compression, sensory disturbance, hypotonia, sciatica.

Psychiatric Disorders: Aggression, affect lability, anger, bruxism, confusional state, crying, depersonalization, depressed mood, depressive symptom, disturbance in sexual arousal, early morning awakening, euphoric mood, feeling of despair, feelings of worthlessness, hallucination, auditory hallucination, altered mood, mood swings, nervousness, abnormal orgasm, paranoia, sleep disorder, tension, thinking abnormal, trichotillomania, libido decreased, nightmare, restlessness, panic reaction, disorientation, hostility, psychomotor agitation, stress symptoms, apathy, delusion, mood altered, perseveration, sleep walking, social avoidant behaviour.

Renal and Urinary Disorders: Micturition urgency, urethral pain, dysuria, hypertonic bladder, micturition disorder, polyuria, renal pain, urinary incontinence.

Reproductive System and Breast Disorders: Metrorrhagia, menstruation irregular, amenorrhoea, genital rash, premenstrual syndrome, erectile dysfunction, menstrual disorder, breast tenderness, testicular pain, breast microcalcification, breast hypertrophy, nipple pain, ovarian cyst, vaginal haemorrhage.

Respiratory, Thoracic, and Mediastinal Disorders: Asthma, dyspnoea, epistaxis, increased upper airway secretion, respiratory tract congestion, rhinorrhoea, sinus disorder, sneezing, throat irritation, vocal cord disorder, yawning, sinus pain, hyperventilation, snoring, nasal dryness, pleuritic pain, pulmonary congestion, wheezing.

Skin and Subcutaneous Tissue Disorders: Alopecia, cold sweat, dermal cyst, dry skin, increased tendency to bruise, night sweats, photosensitivity reaction, rash erythematous, skin irritation, urticaria, eczema, facial oedema, hypotrichosis, pruritus generalized, swelling face, circumoral oedema, allergic dermatitis, rash pruritic, sebaceous gland disorder.

Vascular Disorders: Flushing, peripheral coldness.

Events Observed During Development and Post-Marketing Experience of Bupropion with Other Formulations or Indications

In addition to the events noted above for bupropion hydrochloride extended-release tablets, the following adverse events 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.

Seizures

Post-marketing reports suggest that the reintroduction of bupropion hydrochloride sustained-release tablets in patients who experienced a seizure is associated with a risk of seizure reoccurrence in some cases. Thus, patients should not restart bupropion hydrochloride **sustained-release tablets** therapy if they have had a seizure on a formulation containing bupropion hydrochloride. See WARNINGS AND PRECAUTIONS.

At doses of bupropion hydrochloride sustained-release tablets up to a dose of 300 mg/day, the incidence of seizure is approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1000) at a dose of 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 225 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. The 600 mg dose is twice the adult dose of bupropion hydrochloride extended-release tablets. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

Adverse Events Associated with Discontinuation of Treatment with Other formulations
In placebo-controlled studies of depression with bupropion hydrochloride sustained-release tablets (987 patients treated, and 385 treated with placebo) adverse events caused discontinuation in 7% of bupropion hydrochloride sustained-release tablets-treated patients and 3% of placebo-treated patients. The more common events leading to discontinuation of bupropion hydrochloride sustained-release tablets included nervous system disturbances (2.2%), primarily agitation, anxiety and insomnia; skin disorders (1.9%), primarily rashes, pruritis, and urticaria ; general body complaints (1.0%), primarily headaches, and digestive system disturbances (1.0%), primarily nausea. Two patients in bupropion hydrochloride sustained-release tablets 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.

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated with Bupropion hydrochloride sustained-release tablets (BUP SR) in placebo controlled trials:
Table 3 enumerates treatment-emergent adverse events that occurred at an incidence of 1% or more and were more frequent than in the placebo group, in patients participating in placebo-controlled clinical trials. Reported adverse events were classified using a COSTART-based Dictionary.

TABLE 3 - ADVERSE EVENTS (%)
Treatment-Emergent Adverse Experiences Occurring in ≥1% of Patients in Any BUP SR Group for 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)
Body (General)	Asthenia	1.8	1.6	1.6
	Flu Syndrome	6.2	2.4	3.1
	Headache	27.5	26.9	23.4

Body System	Adverse Experience	% AEs BUP SR 100-150 (n=382)	% AEs BUP SR 200-300 (n=491)	% AEs PBO (n = 385)
	Infection	4.7	7.5	6.5
	Accidental Injury	1.8	1.8	1.8
	Pain	1.3	2.4	2.1
	Abdominal Pain	3.9	3.5	1.6
	Back Pain	1.8	4.5	3.1
	Chest Pain	1	2.9	0.8
	Neck Pain	1.3	2	1.3
Cardiovascular	Hot Flashes	1.3	1	0.8
	Migraine	0.8	1.4	1
	Palpitations	2.9	2	1.6
	Tachycardia	1.6	0.6	0.5
Digestive	Anorexia	3.1	4.5	1.6
	Constipation	6.5	10.8	6.8
	Diarrhoea	3.9	5.9	5.7
	Dry Mouth	13.1	16.5	7
	Dyspepsia	4.2	4.7	4.4
	Flatulence	1.8	3.1	2.1
	Nausea	10.7	12.6	7.5
	Vomiting	1.8	3.9	1.6
Musculoskeletal	Arthralgia	2.6	0.8	0.5
	Leg Cramps	1	0.2	0.5
	Myalgia	1.6	3.3	2.9
	Twitch	0.8	1	0.3
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

Body System	Adverse Experience	% AEs BUP SR 100-150 (n=382)	% AEs BUP SR 200-300 (n=491)	% AEs PBO (n = 385)
	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

In an open label, uncontrolled (acute treatment and continuation) study of bupropion hydrochloride sustained-release tablets, 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 bupropion hydrochloride sustained-release tablets.

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-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 bupropion hydrochloride sustained-release Tablets (n = 3100). All treatment-emergent adverse events are included except those listed in Table 3, 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.

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 bupropion hydrochloride sustained-release tablets is unknown.

Body (General): Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise.

Cardiovascular: Infrequent were postural hypotension, stroke and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS, Cardiovascular Effects), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal haemorrhage, gum haemorrhage, 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 and muscle weakness.

Nervous System: Infrequent were abnormal coordination, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypesthesia, suicidal ideation, 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.

Respiratory: Rare was bronchospasm/dyspnea. Also observed was pneumonia and epistaxis.

Skin/Hypersensitivity: Rare was maculopapular rash. Also observed were alopecia, hirsutism, angioedema, exfoliative dermatitis, erythema multiforme, and Stevens-Johnson syndrome. Arthralgia, myalgia and fever have also been reported in association with rash and other

symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness.

Special Senses: 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.

Post-marketing reports suggest that the reintroduction of bupropion hydrochloride sustained-release tablets in patients who experienced a seizure is associated with a risk of seizure reoccurrence in some cases. Thus, patients should not restart bupropion hydrochloride **sustained-release tablets** therapy if they have had a seizure on a formulation containing bupropion hydrochloride. See WARNINGS AND PRECAUTIONS.

DRUG INTERACTIONS

Overview

In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme (see ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics). Therefore, the potential exists for a drug interaction between TEVA-BUPROPION XL 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 bupropion hydrochloride sustained-release tablets 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).

Drug-Drug Interactions

Drugs Metabolized By CYP2D6:

Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg

twice daily, followed by a single dose of 50 mg desipramine, increased the Cmax, AUC, and t1/2 of desipramine by an average of approximately two-, five- and two-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

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

Tamoxifen

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

Citalopram

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

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

Co-administration of Thioridazine Contraindicated

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

elevate plasma levels of thioridazine. Therefore concomitant use of thioridazine with TEVA-BUPROPION XL is contraindicated (see CONTRAINDICATIONS).

Co-administration of other drugs metabolized by CYP2D6 isoenzyme

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

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

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

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

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

Clopidogrel and Ticlopidine:
Both clopidogrel and ticlopidine have been shown to significantly inhibit CYP2B6-catalysed bupropion hydroxylation. The mean area under the plasma concentration-time curve (AUC) of

hydroxybupropion was reduced by 52% by clopidogrel and by 84% by ticlopidine. The AUC of bupropion was increased by 60% with clopidogrel and by 85% with ticlopidine. Therefore, concomitant administration of bupropion and either clopidogrel or ticlopidine results in increased plasma concentrations of bupropion and reduced concentrations of hydroxybupropion. This may affect the efficacy of bupropion and may also increase the risk of concentration-dependent adverse events of bupropion, such as seizures (see WARNINGS AND PRECAUTIONS, Seizures). Patients receiving either clopidogrel or ticlopidine are likely to require dose adjustments of bupropion.

Digoxin:
Co-administration of digoxin with bupropion may decrease digoxin levels. 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. Caution is advised when concomitant administration of TEVA-BUPROPION XL and digoxin is required.

Use of* TEVA-BUPROPION XL with *Drugs that Predispose Patients to Seizures:
Concurrent administration of TEVA-BUPROPION XL 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 WARNINGS AND PRECAUTIONS). Low initial dosing and gradual dose increases should be employed.

Other Drugs with CNS Activity:
The risk of using bupropion hydrochloride extended-release tablets in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of TEVA-BUPROPION XL and such drugs is required.

Transdermal Nicotine Interaction*:*
(see WARNINGS AND PRECAUTIONS, Cardiovascular Effects)

Alcohol Interactions*:*

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

DOSAGE AND ADMINISTRATION

TEVA-BUPROPION XL (bupropion hydrochloride) is not indicated for use in children under 18 years of age. (See WARNINGS AND PRECAUTIONS: POTENTIAL

ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

Recommended Dose and Dosage Adjustment:

Major Depressive Disorder

Dosing with TEVA-BUPROPION XL Tablets should begin at 150 mg/day given as a single daily dose in the morning. The dose of TEVA-BUPROPION XL may be increased to the 300 mg/day maximum dose as early as 1 week after initiation of treatment. The usual adult target dose for TEVA-BUPROPION XL Tablets is 300 mg/day, given once daily in the morning. The dose can be reduced to, or maintained at 150 mg daily if the patient is unable to tolerate the 300 mg/day dose.

Prevention of Seasonal Major Depressive Episodes

TEVA-BUPROPION XL should be initiated in the autumn prior to the onset of depressive symptoms. Treatment should continue through the winter season and should be tapered and discontinued in early spring. The timing of initiation and duration of treatment should be individualized based on the patient's historical pattern of seasonal major depressive episodes. Patients whose seasonal depressive episodes are infrequent or not associated with significant impairment should generally not be treated prophylactically.

Dosing with TEVA-BUPROPION XL Tablets should begin at 150 mg/day given as a single daily dose in the morning. The dose of TEVA-BUPROPION XL may be increased to the 300mg/day maximum dose after 1 week. The usual adult target dose for TEVA-BUPROPION XL Tablets is 300 mg/day, given once daily in the morning. The dose can be reduced to, or maintained at 150 mg daily if the patient is unable to tolerate the 300 mg/day dose. For patients taking 300 mg/day during the autumn-winter season, the dose should be tapered to 150 mg/day for 2 weeks prior to discontinuation.

Doses of bupropion hydrochloride extended-release tablets above 300 mg/day have not been studied for the prevention of seasonal major depressive episodes.

Missed Dose

TEVA-BUPROPION XL should be taken at the same time each day and no more than one 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.

Administration

Patients should be advised to swallow TEVA-BUPROPION XL 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**.**

When switching patients from bupropion hydrochloride sustained-release tablets to TEVA-BUPROPION XL, give the same total daily dose when possible (for example 150 mg bupropion hydrochloride sustained-release tablets twice a day may be switched to 300 mg TEVA-

BUPROPION XL once daily). TEVA-BUPROPION XL should never be taken concurrently with other medications containing bupropion.

Treatment of Pregnant Women During the Third Trimester
Post-marketing reports indicate that some neonates exposed to bupropion hydrochloride sustained-release tablets, SSRIs, or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with TEVA-BUPROPION XL during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering TEVA-BUPROPION XL 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 elderly or debilitated (see WARNINGS AND PRECAUTIONS). 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 TEVA-BUPROPION XL should be initiated at the lowest recommended dose (150 mg/day).

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 TEVA-BUPROPION XL 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 bupropion hydrochloride extended-release tablets in hepatically impaired patients (see also WARNINGS AND PRECAUTIONS).

Severe Impairment: Given the risks associated with both peak bupropion levels and drug accumulation, TEVA-BUPROPION XL is not recommended for use in patients with severe hepatic impairment. However, should clinical judgement deem it necessary, the drug should be used only with extreme caution (see also WARNINGS AND PRECAUTIONS). The dose should not exceed 150 mg every 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 ACTIONS AND CLINICAL PHARMACOLOGY; WARNINGS AND PRECAUTIONS).

Renal Impairment:
TEVA-BUPROPION XL 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 ACTIONS, and CLINICAL PHARMACOLOGY, and WARNINGS AND PRECAUTIONS).

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.

***Pediatrics*:**
TEVA-BUPROPION XL is not indicated for use in children under 18 years of age (see INDICATION and WARNINGS AND PRECAUTIONS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

OVERDOSAGE

Human Overdose Experience:
In addition to those events reported under *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. No overdoses occurred during bupropion hydrochloride extended-release tablets clinical trials. Three overdoses with bupropion hydrochloride sustained-release tablets occurred during clinical trials. One patient ingested 3000 mg of bupropion hydrochloride sustained-release tablets and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a "handful" of bupropion hydrochloride sustained-release tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3,600 mg of bupropion hydrochloridesustained-release 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 bupropion hydrochloride and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

Since introduction, overdoses of up to 17,500 mg of the immediate release formulation of bupropion hydrochloride, and up to 10,500 mg of bupropion hydrochloride extended-release tablets have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of bupropion hydrochloride or bupropion hydrochloride extended-release tablets alone included hallucinations, loss of consciousness, respiratory arrest, amnesia, and sinus tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, respiratory failure, delirium, and cerebral edema have been reported when bupropion hydrochloride or bupropion hydrochloride extended-release tablets was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion hydrochloride alone have been reported rarely in patients ingesting large doses of

bupropion hydrochloride 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 TEVA-BUPROPION XL 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.

Management of Overdose:

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

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. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

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

Due to the dose-related risk of seizures with TEVA-BUPROPION XL, 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).

ACTION AND CLINICAL PHARMACOLOGY

TEVA-BUPROPION XL (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.

Mechanism of Action

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.

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 Adverse Events).

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.

Pharmacokinetics

Absorption:

Bupropion has not been administered intravenously to humans; therefore, the absolute bioavailability of bupropion hydrochloride extended-release tablets in humans has not been determined. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%. Following oral administration of bupropion hydrochloride sustained-release tablets 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.

In a single-dose study, food increased the C_{max} of bupropion by 11% and the extent of absorption as defined by area under the plasma concentration-time curve (AUC) by 17%. The mean time to peak concentration (t_{max}) was prolonged by 1 hour. This effect was of no clinical significance.

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 CYP2B6 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 WARNINGS AND PRECAUTIONS: Drug Interactions).

Excretion:
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 bupropion hydrochloride sustained-release tablets 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 14C-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:
The pharmacokinetics of buproprion hydrochloride extended-release tablets in individuals under 18 years old has not been evaluated.

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

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 WARNINGS AND PRECAUTIONS, see DOSAGE AND ADMINISTRATION).

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.

STORAGE AND STABILITY
Store at controlled room temperature (15 – 30°C). Keep in a safe place out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

TEVA-BUPROPION XL Extended-Release Tablets are formulated for oral administration and are available as 150 mg and 300 mg tablets with the following descriptions:
TEVA-BUPROPION XL 150 mg tablets are supplied as white to off-white, round, bi-convex, film coated tablets with a black imprint stating WPI and 3331 on one side and plain on the other side.

TEVA-BUPROPION XL 300 mg tablets are supplied as white to off-white, round, bi-convex, film coated tablets with a black imprint stating WPI and 3332 on one side and plain on the other side.

Composition

Each tablet contains bupropion hydrochloride as the active ingredient and the following inactive ingredients: Hydroxypropyl Cellulose, Silicified Microcrystalline Cellulose, Stearic Acid.

The tablet film coating contains: Ethylcellulose, Hydroxypropyl Cellulose, Methacrylic Acid Copolymer, Talc, Titanium Dioxide and Triethyl Citrate.

The tablet imprinting contains: Hypromellose, Iron Oxide Black, Isopropyl Alcohol and

Propylene Glycol.

Packaging

TEVA-BUPROPION XL 150 mg and 300 mg tablets are available in HDPE bottles of 90 tablets and 500 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

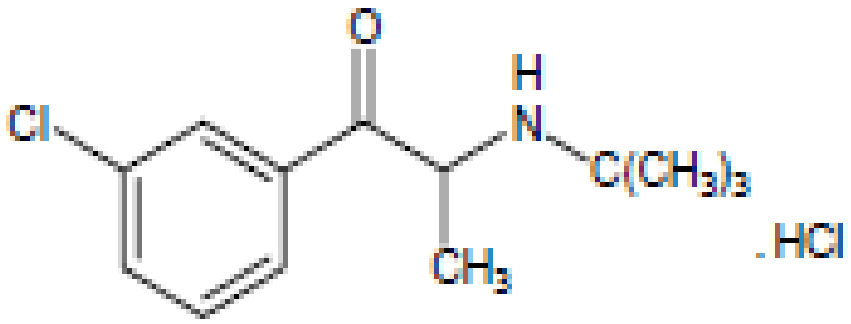
Proper name: Bupropion Hydrochloride

Chemical name: (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1- propanone hydrochloride
(±)-2-(*tert*-Butylamino)-3'-chloropropiophenone hydrochloride

Molecular formula: $C_{13}H_{18}ClNO \bullet HCL$

Molecular mass: 276.21 g/mol

Structural formula:



Physicochemical properties: White or almost white crystalline powder

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, double-blinded, two treatment, two period, two sequence, single dose (1 x 150 mg) crossover bioequivalence study comparing TEVA-BUPROPION XL (bupropion hydrochloride) extended-release tablets, 150 mg (Teva Canada Limited) and WELLBUTRIN® XL (bupropion hydrochloride) extended-release tablets, 150 mg (Biovail Pharmaceuticals Canada), was conducted in 42 healthy, adult volunteers under fasting conditions. Comparative bioavailability data from 40 subjects that were included in the statistical analysis are presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Bupropion
(1 x 150 mg bupropion hydrochloride)
Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·hr/mL)	688.8 707.0 (22.7)	767.9 802.0 (29.1)	89.7	85.0 - 94.8
AUC_I (ng·hr/mL)	728.7 747.4 (22.4)	809.5 844.0 (28.5)	90.1	85.3 - 95.1
C_{MAX} (ng/mL)	65.5 68.510 (29.2)	72.7 76.5 (32.2)	90.2	82.5 - 98.7
T_{MAX}§ (h)	4.5 (3.0 – 7.5)	5.01 (3.0 – 7.0)		
$T_{½}$€ (h)	20.7 (43.4)	20.4 (41.6)		

* TEVA-BUPROPION XL (bupropion hydrochloride) extended-release tablets, 150 mg (Teva Canada Limited).

† WELLBUTRIN® XL (bupropion hydrochloride) extended-release tablets, 150 mg (Biovail Pharmaceuticals Canada).

§ Expressed as median (range).

€ Expressed as the arithmetic mean (CV%) only.

A randomized, double-blinded, two treatment, two period, two sequence, single dose (1 x 150 mg) crossover bioequivalence study comparing TEVA-BUPROPION XL (bupropion hydrochloride) extended-release tablets, 150 mg (Teva Canada Limited) and WELLBUTRIN® XL (bupropion hydrochloride) extended-release tablets, 150 mg (Biovail Pharmaceuticals Canada) was conducted in 36 healthy, adult volunteers under fed conditions. Comparative bioavailability data from 34 subjects that were included in the statistical analysis are presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Bupropion
(1 x 150 mg bupropion hydrochloride)
Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·hr/mL)	934.6 964.3 (27.1)	953.6 983.4 (26.5)	98.2	94.6 – 101.9
AUC_I (ng·hr/mL)	973.3 1003.8 (26.8)	988.4 1018.7 (26.2)	98.7	95.1 - 102.4
C_{MAX} (ng/mL)	77.8 80.7 (28.4)	76.7 78.6 (23.9)	101.5	95.0 - 108.3
T_{MAX}§ (h)	5.5 (4.5 – 10.0)	6.0 (4.5 – 10.0)		
$T_{½}$€ (h)	19.6 (38.7)	19.8 (35.4)		

* TEVA-BUPROPION XL (bupropion hydrochloride) extended-release tablets, 150 mg (Teva Canada Limited).

† WELLBUTRIN® XL (bupropion hydrochloride) extended-release tablets, 150 mg (Biovail Pharmaceuticals Canada).

§ Expressed as median (range).

€ Expressed as the arithmetic mean (CV%) only.

A randomized, blinded, three treatment, three period, single dose (1 x 300 mg) crossover bioequivalence study comparing TEVA-BUPROPION XL (bupropion hydrochloride) extended-release tablets, 300 mg (Teva Canada Limited) and WELLBUTRIN® XL (bupropion hydrochloride) extended-release tablets, 300 mg (Biovail Pharmaceuticals Canada) was conducted in 18 healthy, adult volunteers under fasting conditions. Comparative bioavailability data from 18 subjects that were included in the statistical analysis are presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Bupropion
(1 x 300 mg bupropion hydrochloride)
Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means[1]	90% Confidence Interval
AUC_T (ng·hr/mL)	1457.9 1533.0 (34.1)	1474.0 1609.4 (41.17)	98.9	86.2 - 113.6
AUC_I (ng·hr/mL)	1504.9 1578.9 (33.5)	1526.3 1664.8 (40.9)	98.5	85.9 - 113.1
C_{MAX} (ng/mL)	123.8 132.2 (36.2)	145.2 153.2 (34.9)	85.3	74.8 - 97.3
T_{MAX}§ (h)	4.6 (20.2)	4.6 (19.2)		
$T_{½}$§ (h)	21.5 (36.4)	21.7 (38.5)		

* TEVA-BUPROPION XL (bupropion hydrochloride) extended-release tablets, 300 mg (Teva Canada Limited).

† WELLBUTRIN® XL (bupropion hydrochloride) extended-release tablets, 300 mg (Biovail Pharmaceuticals Canada).

§ Expressed as the arithmetic mean (CV%) only.

A randomized, double-blinded, two treatment, two period, two sequence, single dose (1 x 300 mg) crossover bioequivalence study comparing TEVA-BUPROPION XL (bupropion hydrochloride) extended-release tablets, 300 mg (Teva Canada Limited) and WELLBUTRIN® XL (bupropion hydrochloride) extended-release tablets, 300 mg (Biovail Pharmaceuticals Canada) was conducted in 24 healthy, adult volunteers under fed conditions. Comparative bioavailability data from 23 subjects that were included in the statistical analysis are presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Bupropion
(1 x 300 mg bupropion hydrochloride)
Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·hr/mL)	1670.2 1718.5 (23.1)	1699.3 1761.5 (26.8)	98.5	95.4 - 101.6
AUC_I (ng·hr/mL)	1732.4 1780.9 (22.8)	1762.0 1828.3 (27.3)	98.5	95.6 - 101.5
C_{max} (ng/mL)	135.2 138.6 (22.6)	140.3 145.7 (28.2)	96.6	90.3 - 103.4
T_{max}§ (hr)	5.5 (4.5-10.0)	5.5 (4.5-10.0)		
$T_{½}$€ (hr)	27.6 (22.0)	27.4 (23.8)		

* TEVA-BUPROPION XL (bupropion hydrochloride) extended-release tablets, 300 mg (Teva Canada Limited).
† WELLBUTRIN® XL (bupropion hydrochloride) extended-release tablets, 300 mg (Biovail Pharmaceuticals Canada).
§ Expressed as median (range).
€ Expressed as the arithmetic mean (CV%) only.

Safety and Efficacy Trials

MAJOR DEPRESSIVE DISORDER

Study Demographics and Trial Design

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n= number)	Mean age (range)	Gender (M/F)
AK130926	Randomised, double-blind, double-dummy, parallel group Placebo escitalopram	Bupropion hydrochloride extended-release tablets-300-450mg/day (450 mg was taken in two divided doses - 300mg am. dose followed 8 hours later by 150mg dose), po escitalopram Placebo 8 week treatment period	Bupropion hydrochloride extended-release tablets n=135 Placebo n=132	Bupropion hydrochloride extended-release tablets 18-65 Placebo 18-62	Bupropion hydrochloride extended-release tablets 59/76 Placebo 56/76
AK130927	Randomised, double-blind, double-dummy, parallel group Placebo escitalopram	Bupropion hydrochloride extended-release tablets-300-450mg/day (450 mg was taken in two divided doses - 300mg am. dose followed 8 hours later by 150mg dose), po Escitalopram-10-20mg/day, once-a-day, po Placebo 8 week treatment period	Bupropion hydrochloride extended-release tablets n=141 Placebo n=141	Bupropion hydrochloride extended-release tablets 19-71 Placebo 19-73	Bupropion hydrochloride extended-release tablets 56/85 Placebo 53/88
AK130931	Multicentre parallel group, double-blind, randomized Placebo	Bupropion hydrochloride extended-release tablets-300-450mg/day (450mg as a single dose or in divided doses- 300mg am. dose followed 8 hours later by 150mg dose), po Placebo 8 week treatment period	Bupropion hydrochloride extended-release tablets n=135 Placebo n=139	Bupropion hydrochloride extended-release tablets 20-68 Placebo 19-69	Bupropion hydrochloride extended-release tablets 46/89 Placebo 43/96

The three treatment groups, as well as the total population (across all three studies), were comparable with respect to demographic characteristics. The majority of the subjects across the

treatment groups were Female (61%), White (71%), with a mean age of 37 years. The three treatment groups were also similar with respect to height, weight, and BMI.

Study Results

Results of Studies AK130926 and 130927

As studies AK130926 and 130927 were identical in design, analyses of pooled data from the two studies were performed.

Efficacy at Week 8 LOCF

When all the efficacy variables are taken into consideration, pooled data from studies AK130926 and AK130927 shows a consistently greater efficacy for bupropion hydrochloride extended-release tablets formulation group than placebo group, with regard to Major Depressive Disorder. Bupropion hydrochloride extended-release tablets group demonstrated superiority over placebo group with regard to HAMD, CGI, HAD, and MEI assessments at Week 8(LOCF and Observed) and at Week 4(LOCF). The bupropion hydrochloride extended-release tablets group demonstrated statistical superiority over placebo group in ITT population as well as in the target dose population (300mg/day).

Results of Study AK130931

For the primary efficacy endpoint, subjects in bupropion hydrochloride extended-release formulation group exhibited significant improvement over placebo group for overall depressive symptoms measured as mean change from randomisation in IDS-SR (LOCF p=0.018). Significant improvement was also demonstrated in total scores for IDS-C (LOCF p<0.001) and in the subscale of IDS-SR pertaining to pleasure, energy, and interest (LOCF p=0.007).

The mean change from randomisation in IDS-SR total score at Week 8 (Observed) for the bupropion hydrochloride extended-release tablets group was statistically significantly greater (bupropion hydrochloride extended-release formulation mean=-24.4 vs. placebo=-19.3, p=0.005) than that in placebo group.

PREVENTION OF SEASONAL MAJOR DEPRESSIVE EPISODES

Study Demographics and Trial Design

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n= number)	Mean age (range)	Gender (M/F)
AK130930	Multicentre, Randomized, double-blind	Bupropion hydrochloride extended-release tablets 150 – 300 mg/day po	Bupropion hydrochloride extended-release tablets n= 140	Bupropion hydrochloride extended-release tablets 42.1 (19 – 71)	Bupropion hydrochloride extended-release tablets 35 / 105
	Placebo	7 months treatment	Placebo n=132	Placebo 43.0 (22 – 68)	Placebo 37 / 95

AK130936	Multicentre, Randomized, double-blind Placebo	Bupropion hydrochloride extended-release tablets 150 – 300 mg/day po 7 months treatment	Bupropion hydrochloride extended-release tablets n=156 Placebo n=150	Bupropion hydrochloride extended-release tablets 41.8 (20 – 78) Placebo 42.7 (22 – 78)	Bupropion hydrochloride extended-release tablets 53 / 103 Placebo 46 / 104
100006	Multicentre, Randomized, double-blind Placebo	Bupropion hydrochloride extended-release tablets 150 – 300 mg/day po 7 months treatment	Bupropion hydrochloride extended-release tablets n=238 Placebo n=226	Bupropion hydrochloride extended-release tablets 41.2 (19 – 69) Placebo 40.9 (18 – 70)	Bupropion hydrochloride extended-release tablets 74 / 164 Placebo 68 / 158

Results of studies AK130930 and AK130936 and 100006

The efficacy of bupropion hydrochloride extended-release tablets for the prevention of seasonal major depressive episodes was established in 3 double-blind, placebo-controlled trials in adult outpatients with a history of major depressive disorder with an autumn-winter seasonal pattern (as defined by DSM-IV criteria). Treatment was initiated prior to the onset of symptoms in the autumn (September to November) and was discontinued following a 2 week taper that began the first week of spring (fourth week of March), resulting in treatment duration of approximately 4 to 6 months for the majority of patients. At the start of the study, patients were randomized to receive placebo or bupropion hydrochloride extended-release tablets 150 mg once daily for 1 week, followed by up-titration to 300 mg once daily. Patients who were deemed by the investigator to be unlikely or unable to tolerate 300 mg once daily were allowed to remain on, or had their dose reduced to, 150 mg once daily. The mean bupropion hydrochloride extended-release tablets doses in the 3 studies ranged from 257 to 280 mg/day.

In these 3 trials, the percentage of patients who were depression-free at the end of treatment was significantly higher for bupropion hydrochloride extended-release tablets than for placebo: 81.4% vs 69.7%, 87.2% vs 78.7% and 84.0% vs 69.0% for Study 1, 2 and 3, respectively, with a depression-free rate for the 3 studies combined of 84.3% vs 72.0%.

DETAILED PHARMACOLOGY

Pharmacology:

Bupropion is a novel, atypical antidepressant with mild CNS activating properties. Recent data suggest that a significant contribution to the pharmacology of bupropion is made by one of its two major metabolites, hydroxybupropion. Both bupropion and hydroxybupropion are effective in animal models used to predict antidepressant activity in man. Their antidepressant activity appears to be noradrenergically mediated and based on their ability to block norepinephrine (NE) uptake.

As with other antidepressants, bupropion and hydroxybupropion reduce firing rates of NA 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).

Bupropion and its metabolites weakly but selectively inhibited DA uptake into synaptosomes obtained from rat and mouse striatum at concentrations much higher than are achieved in the plasma of patients receiving 450 mg of bupropion. Bupropion and hydroxybupropion had comparable potencies as inhibitors of [^{3}H]-l-NA uptake into synaptosomes obtained from either mouse or rat hypothalamus. The *threo*-aminoalcohol metabolite was 2- to 3-fold weaker (IC_{50} = 10-16 μM). The plasma level of hydroxybupropion achieved in patients is sufficiently high to solely account for the inhibition of NA uptake.

In vitro, bupropion and its metabolites had essentially no affinity for β-adrenergic, DA, GABA, benzodiazepine, 5-HT_{1A}, glycine and adenosine receptors and only weakly inhibited α-adrenergic receptors in rat brain, α_2-adrenergic, 5-HT_2, and muscarinic cholinergic receptors.

Pharmacodynamics:
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 ED50) 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.

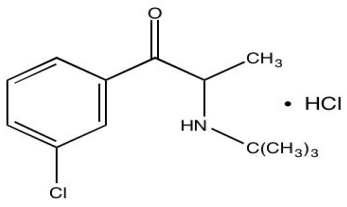
Oral administration of high doses did not produce deleterious cardiovascular effects in conscious dogs (25 mg/kg) and normotensive rats (25-50 mg/kg). Weak, transient dose-dependent effects on the pressor responses to exogenous NA and tyramine were seen in anaesthetized dogs; bupropion was approximately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

Pharmacokinetics:
Preclinical metabolism and disposition studies involving bupropion were conducted in mice, rats, rabbits, and dog. More recent toxicokinetic studies comparing sustained release formulation materials to the immediate release ingredients were done in rats.

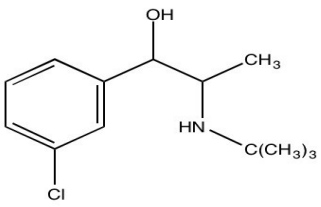
Qualitatively, animals (mouse, rat, rabbit, dog) produce the same metabolites present in man (see structures below), but quantitatively, there are distinct differences with the mouse being most

similar to humans. In animal models, pharmacologic activity (relative to bupropion) of the basic metabolites was 57% for hydroxybupropion (306U73) and 21 % for the isomeric metabolites, erythrohydrobupropion (484U73) and threohydrobupropion (17U67). The acidic metabolites, *m*-chlorobenzoic and *m*-chlorohippuric acids possess no relevant pharmacologic activity. In man, at therapeutic doses, steady state levels of the major metabolite, hydroxybupropion, are 10 to 20-fold greater (AUC and C_{max}) than bupropion levels. Ratios of similar magnitude can occur in animals upon repeated dosing, but as a result of the induction of bupropion metabolism causing a great reduction in parent drug concentrations rather than increased metabolite levels. Such induction has not been observed in man. Bupropion and its metabolites have half-lives in man of 20-40 hr., while 1-2 hr is typical of half-lives in animals. The isomeric metabolites erythrohydrobupropion and threohydrobupropion can be observed in these animal species, but attain plasma concentrations much lower than bupropion or hydroxybupropion. In man, the isomers are of intermediate presence, lower than hydroxybupropion, but similar to or higher than bupropion. It is apparent that no common laboratory animal species has reflected the disposition of bupropion in man.

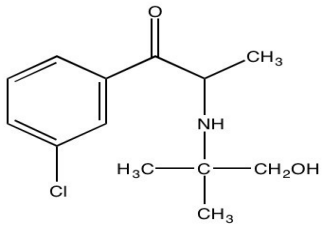
Structures



Bupropion HCl



17U67 (Erythro)
484U73 (Threo)



306U73

In vitro metabolism of bupropion was determined in human microsomal preparations and in cDNA-expressed human cytochrome P450 isozymes. The samples were assayed for parent drug and metabolites by HPLC and LC-MS. Bupropion was mainly metabolized to hydroxybupropion and the threo-amino alcohol metabolite in human microsomal preparations. Meta-chlorobenzoic acid was also formed but in relative minor amounts. The erythro-amino alcohol metabolite of bupropion was not detected.

In the studies using cDNA-expressed systems, hydroxybupropion was produced primarily by the CYP2B6 isozyme, although CYP1A2, 2A6, 2C9, 2E1, and 3A4 isozymes also metabolized bupropion at much slower rates. In human liver microsomes, the metabolism of bupropion to hydroxybupropion was significantly (72%) inhibited by orphenadrine, a CYP2B6 inhibitor. Much lower inhibition (23-39%) was observed with other selective inhibitors of CYP1A2, 2A6, 2C9, 2E1, and 3A4 isozymes. CYP1A1 and CYP2D6 (see PRECAUTIONS, Drugs Metabolized by CYP2D6) isozymes were not involved in the metabolism of bupropion.

The metabolism of bupropion to threohydrobupropion was not inhibited significantly by any cytochrome P450 inhibitors, but was strongly inhibited (> 85%) by the carbonyl reductase inhibitor, menadione. In summary, bupropion was metabolized to hydroxybupropion primarily

by the CYP2B6 and appeared to be metabolized to threohydrobupropion by the carbonyl reductase. The pharmacokinetics of bupropion in humans is described further under ACTIONS AND CLINICAL PHARMACOLOGY.

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.

Carcinogenesis and Mutagenesis

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.

Reproduction and Teratology

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 F_1 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 F_1 males. In the F_2 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.

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PART III: CONSUMER INFORMATION

PrTEVA-BUPROPION XL
Bupropion Hydrochloride Extended-Release Tablets

This leaflet is part III of a three-part "Product Monograph" published when TEVA-BUPROPION XL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-BUPROPION XL. Contact your doctor or pharmacist if you have any questions about the drug.

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

ABOUT THIS MEDICATION

What the medication is used for:
TEVA-BUPROPION XL has been prescribed to you by your doctor to:

- relieve your symptoms of depression (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain) OR
- prevent autumn-winter seasonal depression in patients with a history of seasonal depression

What it does:
TEVA-BUPROPION XL is one of a group of drugs called antidepressants. TEVA-BUPROPION XL is thought to block reuptake of chemicals in the brain called *noradrenaline* and *dopamine*, which are linked with depression.

When it should not be used:
Do not take TEVA-BUPROPION XL if you:

- know that you are allergic to bupropion sustained-release formulation, bupropion, or any of the other ingredients in TEVA-BUPROPION XL tablets
- are taking any other medicines which contain bupropion
- have been diagnosed with epilepsy or have a history of seizures
- have or have had an eating disorder, for example binge eating (bulimia) or anorexia
- are usually a heavy drinker who has just stopped or are about to stop drinking
- are taking Monoamine oxidase (MAO) inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide)
- are taking the antipsychotic thioridazine
- have liver or kidney problems
- are pregnant or trying to become pregnant, or if you think that you might be pregnant
- are breast feeding

What the medicinal ingredient is:
Bupropion hydrochloride

What the nonmedicinal ingredients are:
hydroxypropyl cellulose, silicified microcrystalline cellulose and stearic acid. In addition, the tablet film coating contains: ethylcellulose, hydroxypropyl cellulose, methacrylic acid copolymer, talc, titanium dioxide and triethyl citrate. The tablet imprinting contains: hypromellose, iron oxide black, isopropyl alcohol and propylene glycol.

What dosage forms it comes in:
150 mg and 300 mg extended-release tablets

WARNINGS AND PRECAUTIONS

TEVA-BUPROPION XL is a **Once Daily** medication and should not be confused with other bupropion formulations.

During Treatment with these types of medication it is important that you and your doctor have good ongoing communication about how you are feeling.

TEVA-BUPROPION XL is not for use in Children under 18 years of age.

New or Worsened Emotional or Behavioural Problems
Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm, or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately. Close observation by a doctor is necessary in this situation.

Important Warning About The Risk Of Seizures:
The overall incidence of seizure with bupropion hydrochloride extended-release tablets in clinical trials at doses up to 450 mg/day was approximately 0.1%.

BEFORE you use TEVA-BUPROPION XL tell your doctor or pharmacist if you:

- have ever had any fits or seizures in the past
- take other medications that may increase your chance of a seizure, including drugs for depression and some antibiotics
- are taking any prescription or over-the-counter medications, or are planning on taking any prescription or over-the-counter medications during your therapy
- have, or have had an eating disorder, for example binge eating (bulimia) or anorexia nervosa
- have liver problems
- have kidney problems

- take more than the recommended amount of TEVA-BUPROPION XL tablets. TEVA-BUPROPION XL tablets should NOT be used if you are taking any other medications containing bupropion hydrochloride
- have diabetes which is treated with insulin or other medications
- have use over-the-counter diet aids
- have had a serious head injury
- drink alcohol. It is best not to drink alcohol at all or to drink very little while taking TEVA-BUPROPION XL. If you drink a lot of alcohol and suddenly stop, you may increase your chance of having a seizure. Be sure to discuss your use of alcohol with your doctor before you begin taking TEVA-BUPROPION XL
- are pregnant, or thinking about becoming pregnant, or are breastfeeding

Driving vehicles or using machinery:

TEVA-BUPROPION XL may impair your ability to perform tasks requiring judgement or motor and cognitive skills. Until you are reasonably certain that TEVA-BUPROPION XL does not adversely affect your performance you should refrain from driving an automobile or operating hazardous machinery.

Effects on Pregnancy and Newborns

Post-marketing reports indicate that some newborns whose mother took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer anti-depressant, such as bupropion hydrochloride extended-release tablets, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying.

In most cases, the newer anti-depressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the anti-depressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

If you are pregnant and taking an SSRI, or other newer anti-depressant**,** you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting with your doctor.

Angle-Closure Glaucoma:
TEVA-BUPROPION XL can cause an acute attack of glaucoma. Seek immediate medical attention if you experience eye pain, changes in vision, swelling or redness in or around the eye.

INTERACTIONS WITH THIS MEDICATION

If you are taking or have recently been taking other medicines for depression called monoamine oxidase inhibitors (MAOIs) tell your doctor before taking TEVA-BUPROPION XL.

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

- other antidepressants such as citalopram, paroxetine, venlafaxine.
- the antipsychotic thioridazine.
- other medications for mental illness such as haloperidol and risperidone.
- medicines for Parkinson's disease such as levodopa, amantadine or orphenadrine.
- medicines used for epilepsy (such as carbamazepine, phenytoin, or phenobarbitone).
- cyclophosphamide or ifosfamide, drugs mainly used to treat cancer.
- drugs called beta blockers to treat heart conditions.
- medicines to regulate heart rhythm.
- clopidogrel or ticlopidine, drugs used to reduce blood clots.
- nicotine patches to help you stop smoking.
- digoxin used to treat congestive heart failure and a fast heart rate or irregular heart rhythm such as atrial fibrillation (sometimes called "a-fib")
- tamoxifen, a drug to treat breast cancer.
- ritonavir or efavirenz, drugs to treat HIV infection.
- In general, drinking alcoholic beverages should be kept to a minimum or avoided completely while taking TEVA-BUPROPION XL.

PROPER USE OF THIS MEDICATION

Usual dose:
How to take TEVA-BUPROPION XL

- TEVA-BUPROPION XL is formulated to be taken as a single tablet, once-daily.

Major Depressive Disorder:
Dosing with TEVA-BUPROPION XL Tablets should begin at 150 mg/day given as a single daily dose in the morning. The dose of TEVA-BUPROPION XL may be increased to the 300mg/day maximum dose after 1 week. The usual adult target dose for TEVA-BUPROPION XL Tablets is 300 mg/day, given once daily in the morning.

Prevention of Seasonal Depression:

Dosing with TEVA-BUPROPION XL Tablets should begin at 150 mg/day given as a single daily dose in the morning. The dose of TEVA-BUPROPION XL may be increased to the 300mg/day maximum dose after 1 week. The usual adult target dose for TEVA-BUPROPION XL Tablets is 300 mg/day, given once daily in the morning. For patients taking 300 mg/day during the autumn-winter season, the dose should be reduced to 150 mg/day for 2 weeks prior to discontinuation.

- Take your TEVA-BUPROPION XL tablet at the same time each day. If you have any problems with your dosing routine, contact your doctor or pharmacist.
- Swallow your TEVA-BUPROPION XL tablet whole, with fluids. Do not divide, chew or crush tablets.
- Take only the recommended dose prescribed by your doctor. Never increase the dose of TEVA-BUPROPION XL you or those in your care are taking, unless your doctor tells you to.
- The effects of your medication may not be noticeable in the first few days of treatment, and significant improvement may take several weeks. If you are concerned that your medicine is not working, discuss this with your doctor.
- You should talk to your doctor before you stop taking your medication on your own.

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

Missed Dose:
TEVA-BUPROPION XL should be taken at the same time each day and no more than one dose should be taken each day.

If your normal administration time has been missed, the dose should be skipped and administration resumed at the normal administration time of the following day.

Overdose:
If you take too many tablets, you may increase the risk of a fit or seizure(s), or other serious effects, including irregular heart beat, which may be life-threatening. Serotonin syndrome [a combination of most or all of the following; confusion, restlessness, sweating, shaking, shivering, high fever, sudden jerking of the muscles, hallucinations, fast heart beat] has also been reported.

If you think you have taken too much TEVA-BUPROPION XL, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, TEVA-BUPROPION XL can cause some side effects. You may not experience any of them. For most patients these side effects are likely to be minor and temporary. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

The most common side effects of TEVA-BUPROPION XL are:
- dry mouth
- nausea
- constipation
- insomnia
- dizziness
- anxiety
- decreased appetite

Uncommon side effects
These could affect less than one in every 100 people:
- increased appetite
- weight increase
- bloating
- migraine

New or Worsened Emotional or Behavioural Problems
A small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience new or worsened feelings of agitation, hostility or anxiety, or thoughts about suicide. Your doctor should be informed of such changes immediately. Close observation by a doctor is necessary in this situation. See also the WARNINGS AND PRECAUTIONS section.

Effects on Newborns
Some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer antidepressant during pregnancy have shown such symptoms as breathing and feeding difficulties, jitteriness and constant crying. If your baby experiences any of these symptoms, contact your doctor as soon as you can. See WARNINGS AND PRECAUTIONS section for more information.

Serious Side Effects

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Rare	Seizures [loss of consciousness with uncontrollable shaking ("fit"/ "convulsion")]			√*

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Very Rare	Severe allergic reactions[red and lumpy or blistering skin rash, swelling of the face or throat, trouble breathing, collapse, blackout, severe muscle or joint pains]			√*
Very Rare	Liver disorders, including hepatitis and jaundice [symptoms include nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine]		√*	
Very Rare	Poor Blood Glucose control	√		
Very Rare	Inability to urinate		√	
Very Rare	Hallucinations, delusions, paranoid ideation [sensing or believing thing that are not there]		√	
Very Rare	Aggression		√*	
Very Rare	Low sodium level in blood (tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles)		√	
See Warnings and Precautions	New or Worsened Emotional or Behavioural Problems		√*	
See Warnings and Precautions	Rises in Blood Pressure	√		

* If you think you have these side effects, it is important that you seek medical advice from your doctor straight away.

The overall incidence of seizure with bupropion hydrochloride extended-release tablets in clinical trials at doses up to 450 mg/day was approximately 0.1%.

The chance of a seizure happening is higher if you take too much, if you take certain medicines at the same time, if you drink alcohol, or if you are at higher than usual risk of seizures.

This is not a complete list of side effects. For any unexpected effects while taking TEVA-BUPROPION XL contact your doctor or pharmacist.

HOW TO STORE IT

- Keep all medication out of the reach and sight of children.
- Store TEVA-BUPROPION XL at room temperature (15-30°C)
- Keep container tightly closed
- If your doctor tells you to stop taking TEVA-BUPROPION XL please return any leftover medicine to your pharmacist.

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

MORE INFORMATION

If you want more information about TEVA-BUPROPION XL:

- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9

Last revised: May 5, 2021