Initial U.S. Approval: 1985

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS See full prescribing information for complete boxed warning Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking

antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.1) - RECENT MAINR CHANGES --Warnings and Precautions, Neuropsychiatric Adverse Events and Suicide Risk in Smoking Cessation

- INDICATIONS AND USAGE --Bupropion hydrochloride extended-release tablets (XL) are aminoketone antidepressant, indicated for the

- DOSAGE AND ADMINISTRATION

treatment of major depressive disorder (MDD) and prevention of seasonal affective disorder (SAD). Periodically reevaluate long-term usefulness for the individual patient. (1)

• Increase dose gradually to reduce seizure risk. (2.1, 5.3) Periodically reassess the dose and need for maintenance treatment. (2.2)

Major Depressive Disorder:

• Starting dose: 150 mg once daily. Usual target dose: 300 mg once daily (2.2) After 4 days may increase the dose to 300 mg once daily (2.2)

Seasonal Affective Disorder:

• Initiate treatment in the autumn prior to onset of seasonal depressive symptoms. (2.3)

Starting dose: 150 mg once daily. Usual target dose: 300 mg once daily. (2.3)

After one week, may increase the dose to 300 mg once daily. (2.3) Continue treatment through the winter season. (2.3)

Hepatic Impairment: Moderate to severe hepatic impairment: 150 mg every other day (2.6)
 Mild hepatic impairment: Consider reducing the dose and/or frequency of dosing. (2.6, 8.7)

• Consider reducing the dose and/or frequency of dosing. (2.7, 8.6)

--- DOSAGE FORMS AND STRENGTHS -• Extended-release tablets: 150 mg, 300 mg (3)

Current or prior diagnosis of bulimia or anorexia nervosa (4, 5.3) Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, antiepileptic drugs. (4, 5.3) Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with bupropion hydrochloride extended-release tablets (XL) or within 14 days of stopping treatment with propion hydrochloride extended-release tablets (XL). Do not use bupropion

 Known hypersensitivity to bupropion or other ingredients of bupropion hydrochloride extended-release tablets (XL) (4, 5,8)

release tablets (XL) within 14 days of stopping an MAOI intended to treat psychiatric disorders. In

- CONTRAINDICATIONS

addition, do not start bupropion hydrochloride extended-release tablets (XL) in a patient who is being eated with linezolid or intravenous methylene blue. (4, 7.6)

---WARNINGS AND PRECAUTIONS -- Neuropsychiatric Adverse Events During Smoking Cessation: Postmarketing reports of serious or clinically significant neuropsychiatric adverse events have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, ogitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide serve patients attempting to quit smoking with bupropion hydrochloride extended-release tablets (XL for the occurrence of such symptoms and instruct them to discontinue bupropion hydrochloride extended elease tablets (XL) and contact a healthcare provider if they experience such adverse events. (5.2)

Seizure Risk: The risk is dose-related. Can minimize risk by limiting daily dose to 450 mg and gradually increasing the dose. Discontinue if seizure occurs. (4, 5.3, 7.3)

Hypertension: Bupropion hydrochloride extended-release tablets (XL) can increase blood pressure. Monitor blood pressure before initiating treatment and periodically during treatment. (5.4)
 Activation of Mania/Hypomania: Screen patients for bipolar disorder and monitor for these symptoms.

Psychosis and Other Neuropsychiatric Reactions: Instruct patients to contact a healthcare professional

such reactions occur. (5.6) . Angle-Closure Glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.7) ----- ADVERSE REACTIONS ---

Most common adverse reactions are (incidence $\geq 5\%$; $\geq 2\times$ placebo rate): dry mouth, nausea, insomnia, dizziness, pharyngitis, abdominal pain, agitation, anxiety, tremor, palpitation, sweating, tinnitus, myalgia,

To report SUSPECTED ADVERSE REACTIONS, contact TWI Pharmaceuticals, Inc. at 1-844-518-2989 or FDA at I-800-FDA-1088 or www.fda.gov/medwatch.

----DRUG INTERACTIONS -CYP2B6 inducers: Dose increase may be necessary if coadministered with CYP2B6 inducers (e.g., ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital, and phenytoin) based on clinical exposure

but should not exceed the maximum recommended dose. (7.1)

• Drugs metabolized by CYP2D6: Bupropion inhibits CYP2D6 and can increase concentrations of: antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol) and Type 1C antiarrhythmics (e.g., propafenone, flecainide). Consider dose reduction when using with

Drugs that lower seizure threshold: Dose bupropion hydrochloride extended-release tablets (XL) with

Dopaminergic Drugs (levodopa and amantadine); CNS toxicity can occur when used concomitantly with

MAOIs: Increased risk of hypertensive reactions can occur when used concomitantly with bupropion

hydrochloride extended-release tablets (XL), (7.6) Drug laboratory test interactions: Bupropion hydrochloride extended-release tablets (XL) can cause false-

HYDROCHLORIDE

extended-release tablets

USP (XL)

positive urine test results for amphetamines. (7.7) --- USE IN SPECIFIC POPULATIONS

Pregnancy: Use only if benefit outweighs potential risk to the fetus. (8.1)

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIOR

SUICIDALITY AND ANTIDEPRESSANT DRUGS ssants increased the risk of suicidal thoughts and behavior in children, adolescents, an and behavior with antidepressant use in subjects aged 65 and older [see Warnings and Precaution

In natients of all ages who are started on antidepressant therapy, monitor closely for worsening, a for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see Warnings and Precautions (5.1)].

INDICATIONS AND USAGE

Bupropion hydrochloride extended-release tablets (XL) are indicated for the treatment of major depressive disorder (MDD), as defined by the Diagnostic and Statistical Manual (DSM).

The efficacy of the immediate-release formulation of bupropion was established in two 4-week controlled inpatient trials and one 6-week controlled outpatient trial of adult patients with MDD. The efficacy of the sustained-release formulation of bupropion in the maintenance treatment of MDD was established in a longof acute treatment [see Clinical Studies (14.1)]. 1.2 Seasonal Affective Disorder

Runronion hydrochloride extended-release tablets (XL) are indicated for the prevention of seasonal major

depressive episodes in patients with a diagnosis of seasonal affective disorder (SAD). The efficacy of bupropion hydrochloride extended-release tablets (XL) in the prevention of seasonal major enressive enisodes was established in 3 placeho-controlled trials in adult outpatients with a history of MDD with an autumn-winter seasonal pattern as defined in the DSM [see Clinical Studies (14.2)].

DOSAGE AND ADMINISTRATION

To minimize the risk of seizure, increase the dose gradually [see Warnings and Precautions (5.3)]. Bupropion hydrochloride extended-release tablets (XL) should be swallowed whole and not crushed, divided,

Bupropion hydrochloride extended-release tablets (XL) should be administered in the morning and may be taken with or without food.

2.2 Dosage for Major Depressive Disorder (MDD)

recommended starting dose for MDD is 150 mg once daily in the morning. After 4 days of dosing, the dose may be increased to the target dose of 300 mg once daily in the morning. It is generally agreed that acute episodes of depression require several months or longer of antidepressan

extended-release tablets (XL) dose needed for maintenance treatment is identical to the dose that provided an initial response. Periodically reassess the need for maintenance treatment and the appropriate dose for

inded starting dose for SAD is 150 mg once daily. After 7 days of dosing, the dose may be increased

were not assessed in the SAD trials. For the prevention of seasonal MDD episodes associated with SAD, initiate bupropion hydrochloride extended release tablets (XL) in the autumn, prior to the onset of depressive symptoms. Continue treatment through the winter season. Taper and discontinue bupropion hydrochloride extended-release tablets (XL) in early spring. For patients treated with 300 mg per day, decrease the dose to 150 mg once daily before discontinuing bupropio hydrochloride extended-release tablets (XL). Individualize the timing of initiation, and duration of treatmen should be individualized, based on the patient's historical pattern of seasonal MDD episodes.

to the target dose of 300 mg once daily in the morning. Doses above 300 mg of bupropion HCl extended-relea

Switching Patients from WELLBUTRIN Tablets (bupropion hydrochloride tablets) or from WELLBUTRIN SR (bupropion hydrochloride extended-release tablets (SR))

extended-release tablets (XL) or from WELLBUTRIN SR (bupropion hydrochloride extended-release tablets (SR)) to bupropion hydrochloride extended-release tablets (XL), give the same total daily dose when possible. 2.5 To Discontinue Bupropion Hydrochloride Extended-Release Tablets (XL), Taper the Dose then discontinuing treatment in patients treated with bupropion hydrochloride extended-release tablets (XL)

300 mg once daily decrease the dose to 150 mg once daily prior to discontinuation Dosage Adjustment in Patients with Hepatic Impairment patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum dose is 150 mg every other day. In patients with mild hepatic impairment (Child-Pugh score: 5 to 6), consider reducing

equency of dosing [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)] Dose Adjustment in Patients with Renal Impairment Consider reducing the dose and/or frequency of bupropion hydrochloride extended-release tablets (XL) in patients with renal impairment (glomerular filtration rate less than 90 mL/min) [see Use in Specific Populations

Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Antidepressant At least 14 days should elapse between discontinuation of an MAOI intended to treat depression and initiation f therapy with bupropion hydrochloride extended-release tablets (XL). Conversely, at least 14 days sho be allowed after stopping bupropion hydrochloride extended-release tablets (XL) before starting an MAOI antidepressant (see Contraindications (4) and Drug Interactions (7.6)).

2.9 Use of Bupropion Hydrochloride Extended-Release Tablets (XL) with Reversible MAOIs such as

Do not start bupropion hydrochloride extended-release tablets (XL) in a patient who is being treated with a eversible MAOI such as linezolid or intravenous methylene blue. Drug interactions can increase risk of ypertensive reactions. In a patient who requires more urgent treatment of a psychiatric condition, nonpharmacological interventions, including hospitalization, should be considered [see Contraindications (4)]. In some cases, a patient already receiving therapy with bupropion hydrochloride extended-release tablets (XL) or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenou methylene blue treatment are judged to outweigh the risks of hypertensive reactions in a particular patient bupropion hydrochloride extended-release tablets (XL) should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for 2 weeks or until 24 hours after the last tose of linezolid or intravenous methylene blue, whichever comes first. Therapy with bupropion hydrochloride extended-release tablets (XL) may be resumed 24 hours after the last dose of linezolid or intravenous methylene

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or n intravenous doses much lower than 1 mg per kg with bupropion hydrochloride extended-release tablets (XL) is unclear. The clinician should, nevertheless, be aware of the possibility of a drug interaction with such use [see Contraindications (4) and Drug Interactions (7.6)].

DOSAGE FORMS AND STRENGTHS

Bunronion hydrochloride extended-release tablets USP (XL), 150 mg of bupropion hydrochloride, are white film coated tablets printed with "T101" in black ink on one side and plain on the other side. Bupropion hydrochloride extended-release tablets USP (XL), 300 mg of bupropion hydrochloride, are white film coated tablets printed with "T102" in black ink on one side and plain on the other side.

Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients with seizure disorder. Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients with a current or

prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with bupropion hydrochloride extended-release tablets (XL) [see Warnings and Precautions Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients undergoing abrupt

there have been rare spontaneous postmarketing reports of erythema multiforme. Stevens-Johnson Syndrome discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs [see Warnings and Precautions (5.3) and Drug Interactions (7.3)]. The use of MAOIs (intended to treat psychiatric disorders) concomitantly with bupropion hydrochloride extended-release tablets (XL) and consult a healthcare provider if they develop an allergic or anaphylactoid extended-release tablets (XL) or within 14 days of discontinuing treatment with bupropion hydrochloride extended-release tablets (XL) is contraindicated. There is an increased risk of hypertensive reactions when bupropion hydrochloride extended-release tablets (XL) are used concomitantly with MAOIs. The use of ourronion hydrochloride extended-release tablets (XL) within 14 days of discontinuing treatment with an delayed hypersensitivity. MAOI is also contraindicated. Starting bupropion hydrochloride extended-release tablets (XL) in a patient

reated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated *[see* Dosage and Administration (2.9), Warnings and Precautions (5.4) and Drug Interactions (7.6)].

Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients with known hypersensitivity to bupropion or other ingredients of bupropion hydrochloride extended-release tablets (XL). Anaphylactoid/anaphylactic reactions and Stevens-Johnson Syndrome have been reported [see Warnings • Neuropsychiatric adverse events and suicide risk in smoking cessation treatment [see Warnings and

WARNINGS AND PRECAUTIONS Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant emission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these
6.1 Clinical Trials Experience disorders themselves are the strongest predictors of suicide. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in

certain patients during the early phases of treatment. Pooled analyses of short-term placeho-controlled trials of antidepressant drugs (Selective Serotonia Reuntake suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with essants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric both to the immediate-release and sustained-release formulations of bupropion. The information included under this subsection and under subsection 6.2 is based primarily on data from controlled clinical trials with disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (d placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **Table 1**.

Table 1: Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled Placeho-Controlled Trials of Antidenressants in Pediatric and Adult Patients

is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of

All patients being treated with antidepressants for any indication should be monitored appropriately a

observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the

impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and

pediatric patients being treated with antidepressants for major depressive disorder as well as for other

indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such

symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not bee

lished, there is concern that such symptoms may represent precursors to emerging suicidality.

nitial few months of a course of drug therapy, or at times of dose changes, either increases or decreas

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggress

see Boxed Warning and Use in Specific Populations (8.4)].

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated	and at a rate at least twice t	he placebo rate are	listed in Table 2 .	
	Increases Compared to Placebo				
<18 years	14 additional cases	Table 2: Treatment Dis	continuation Due to	Adverse Reactions in Placel	bo-Controlled Trials in MDD
18-24 years	5 additional cases	Adverse Reaction Term	Placebo	Bupropion HCI	Bupropion HCI
	Decreases Compared to Placebo		(n=385)	Sustained-Release	Sustained-Release
25-64 years	1 fewer case			300 mg/day (n=376)	400 mg/day (n=114)
≥65 years	6 fewer cases			(II=3/b)	(11=114)
≥00 years	O TEWEL CASES	Rash	0.0%	2.4%	0.9%
No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was		Nausea	0.3%	0.8%	1.8%
not sufficient to	reach any conclusion about drug effect on suicide.	Agitation	0.3%	0.3%	1.8%
It is unknown wh	ether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there	Migraine	0.3%	0.0%	1.8%

In clinical trials with bupropion HCI immediate-release, 10% of patients and volunteers discontinued due to an adverse reaction. Reactions resulting in discontinuation (in addition to those listed above for the sustainedrelease formulation) included vomiting, seizures, and sleep disturbances. Adverse Reactions Occurring at an Incidence of >1% in Patients Treated with Bupropion HCI Immediate-

Release or Bupropion HCI Sustained-Release in MDD Table 3 summarizes the adverse reactions that occurred in placebo-controlled trials in patients treated with bupropion HCl sustained-release 300 mg/day and 400 mg/day. These include reactions that occurred in either the 300 mg or 400 mg group at an incidence of 1% or more and were more frequent than in the placebo group.

Table 3: Adverse Reactions in Placebo-Controlled Trials in Patients with MDD

Bupropion HCI

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing th

medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidalit

evere, abrupt in onset, or were not part of the patient's presenting symptom

consistent with good patient management, in order to reduce the risk of overdose.

or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are

Families and caregivers of patients being treated with antidepressants for major depressive disorder or

other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients

for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare

providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for

propion hydrochloride extended-release tablets (XL) should be written for the smallest quantity of table

pion hydrochloride extended-release tablets (XL) are not approved for smoking cessation treatment

however, bupropion HCl sustained-release is approved for this use. Serious neuropsychiatric adverse events

have been reported in patients taking bupropion for smoking cessation. These postmarketing reports have

attempt, and completed suicide [see Adverse Reactions (6.2)]. Some patients who stopped smoking may have

een experiencing symptoms of nicotine withdrawal, including depressed mood. Depression, rarely including

uicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication

Neuropsychiatric adverse events occurred in patients without and with pre-existing psychiatric disease

europsychiatric adverse events. Advise patients and caregivers that the patient should stop taking bupropio

essed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the

hydrochloride extended-release tablets (XL) and contact a healthcare provider immediately if agitation

patient develops suicidal ideation or suicidal behavior. The healthcare provider should evaluate the severity

ncluding continued treatment under closer monitoring, or discontinuing treatment. In many postmarketing

cases, resolution of symptoms after discontinuation of bupropion was reported. However, the symptoms

persisted in some cases; therefore, ongoing monitoring and supportive care should be provided until symptom

Bupropion hydrochloride extended-release tablets (XL) can cause seizure. The risk of seizure is dose-related. The

dose should not exceed 300 mg once daily. Increase the dose gradually. Discontinue bupropion hydrochlorid extended-release tablets (XL) and do not restart treatment if the patient experiences a seizure.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that

lower the seizure threshold. Consider these risks before initiating treatment with bupropion hydrochloride extended-release tablets (XL). Bupropion hydrochloride extended-release tablets (XL) are contraindicated

in patients with a seizure disorder or conditions that increase the risk of seizure (e.g., severe head injury

scontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs [see Contraindications (4)]

The following conditions can also increase the risk of seizure: concomitant use of other medications that lower

the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids), metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment

and hypoxia), or use of illicit drugs (e.g., cocaine) or abuse or misuse of prescription drugs such as CNS

cidence of seizure with bupropion hydrochloride extended-release tablets (XL) has not been formally

or insulin, use of anorectic drugs, excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

realizated in clinical trials. In studies using bupropion HCl sustained-release up to 300 mg per day the incidence of seizure was approximately 0.1% (1/1000 patients). In a large prospective, follow-up study, the

seizure incidence was approximately 0.4% (13/3200) with hupropion HCL immediate-release in the range of

increases almost tenfold between 450 and 600 mg/day. The risk of seizure can be reduced if the bupropion

hydrochloride extended-release tablets (XL) dose does not exceed 450 mg once daily and the titration rate i

Treatment with bupropion hydrochloride extended-release tablets (XL) can result in elevated blood pressure

Assess blood pressure before initiating treatment with bupropion hydrochloride extended-release tablets (XL),

and monitor periodically during treatment. The risk of hypertension is increased if bupropion hydrochlorid

xtended-release tablets (XL) are used concomitantly with MAOIs or other drugs that increase dopaminergic o

Data from a comparative trial of the sustained-release formulation of bupropion HCI, nicotine transdermal

system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smokin

cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with th

combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared t 2.5%, 1.6%, and 3.1% of subjects treated with sustained-release bupropion, NTS, and placebo, respectively

medication discontinued due to hypertension compared with none of the subjects treated with sustained

release bupropion or placebo. Monitoring of blood pressure is recommended in patients who receive the

in blood pressure. Hypertension was reported as an adverse reaction for 2% of the bupropion group (11/537) and

one in the placebo group (0/511). In the SAD trials, 2 patients treated with bupropion discontinued from the

study because they developed hypertension. None of the placebo group discontinued because of hypertension

The mean increase in systolic blood pressure was 1.3 mmHg in the bupropion group and 0.1 mmHg in the

lacebo group. The difference was statistically significant (p=0.013). The mean increase in diastolic bloo

pressure was 0.8 mmHg in the bupropion group and 0.1 mmHg in the placebo group. The difference was

not statistically significant (p=0.075). In the SAD trials, 82% of patients were treated with 300 mg per day

and 18% were treated with 150 mg per day. The mean daily dose was 270 mg per day. The mean duration of

In a clinical trial of bupropion immediate-release in MDD subjects with stable congestive heart failur

(N=36), bupropion was associated with an exacerbation of pre-existing hypertension in 2 subjects, leading to discontinuation of bupropion treatment. There are no controlled studies assessing the safety of bupropion in

be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating

bupropion hydrochloride extended-release tablets (XL), screen patients for a history of bipolar disorder and th

upropion hydrochloride extended-release tablets (XL) are not approved for the treatment of bipolar depressio

including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some o

these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction

and/or withdrawal of treatment. Discontinue bupropion hydrochloride extended-release tablets (XL) if the

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drug

including bupropion hydrochloride extended-release tablets (XL) may trigger an angle-closure attack in a

phylactoid/anaphylactic reactions have occurred during clinical trials with bupropion. Reactions hav

been characterized by pruritus, urticaria, angioedema, and dyspnea, requiring medical treatment. In addition

naphylactic reaction (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the

clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not

Commonly Observed Adverse Reactions in Controlled Clinical Trials of Sustained-Release Bupropion

Adverse reactions that occurred in at least 5% of patients treated with bupropion HCl sustained-release (300

400 mg/day of bupropion HCl sustained-release: abdominal pain, agitation, anxiety, dizziness, dry mouth,

Bupropion hydrochloride extended-release tablets (XL) have been demonstrated to have similar bioavailabilit

Adverse Reactions Leading to Discontinuation of Treatment with Bupropion HCI Immediate-Release

Bupropion HCI Sustained-Release, and Bupropion HCI Extended-Release in Major Depressive Disorder Trials

In placebo-controlled clinical trials with bupropion HCl sustained-release, 4%, 9%, and 11% of the placebo, 300 mg/day and 400 mg/day groups, respectively, discontinued treatment because of adverse reactions. The

pecific adverse reactions leading to discontinuation in at least 1% of the 300 mg/day or 400 mg/day group

300 mg/day of hupropion HCl sustained-release apprexia dry mouth rash sweating tipnitus and tremor

insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

and anaphylactic shock associated with bupropion. Instruct patients to discontinue bupropion hydroc

The following adverse reactions are discussed in greater detail in other sections of the labeling

Activation of mania or hypomania (see Warnings and Precautions (5.5)]
 Psychosis and other neuropsychiatric events [see Warnings and Precautions (5.6)]

mg and 400 mg per day) and at a rate at least twice the placebo rate are listed below.

the sustained-release and extended-release formulations of bupropion hydrochloride.

patients treated with bupropion have had a variety of neuropsychiatric signs and symptom

patients with a recent history of myocardial infarction or unstable cardiac disease.

patient with anatomically narrow angles who does not have a patent iridectomy.

he majority of these subjects had evidence of pre-existing hypertension. Three subjects (1.2%) treated with

nation of sustained-release bupropion and NTS and 1 subject (0.4%) treated with NTS had study

ombination of sustained-release bupropion and NTS. In this trial, 6.1% of subjects treated with the

Incidence of Seizure with Bupropion Use

oradrenergic activity [see Contraindications (4)].

bupropion exposure was 126 days.

5.5 Activation of Mania/Hypomania

Angle-Closure Glaucoma

5.8 Hypersensitivity Reactions

6 ADVERSE REACTIONS

Precautions (5.2)]
Seizure [see Warnings and Precautions (5.3)]

reflect the rates observed in practice.

Maior Depressive Disorder

Hypertension [see Warnings and Precautions (5.4)]

Angle-Closure Glaucoma [see Warnings and Precautions (5.7)]

5.6 Psychosis and Other Neuropsychiatric Reactions

nous malformation, CNS tumor or CNS infection, severe stroke, anorexia nervosa or bulimia, or abru

o conditions include diabetes mellitus treated with oral hypoglycemic drug

of the adverse events and the extent to which the patient is benefiting from treatment, and consider option

However, some of these adverse events occurred in patients taking bupropion who continued to smoke.

nicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide

included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusion

Neuropsychiatric Adverse Events and Suicide Risk in Smoking Cessation Treatment

	(11=363)	300 mg/day (n=376)	400 mg/day (n=114)
Body (General)		(11-070)	(111)
Headache	23%	26%	25%
Infection	6%	8%	9%
Abdominal pain	2%	3%	9%
Asthenia	2%	2%	4%
Chest pain	1%	3%	4%
Pain	2%	2%	3%
Fever	276	1%	2%
Cardiovascular	-	1 /0	2/0
Palpitation	2%	2%	6%
Flushing	- 270	1%	4%
Migraine	1%	1%	4%
Hot flashes	1%	1%	3%
	1 /0	1 /0	3/6
Digestive Dry mouth	7%	17%	24%
,			
Nausea	8%	13%	18%
Constipation	7%	10%	5%
Diarrhea	6%	5%	7%
Anorexia	2%	5%	3%
Vomiting	2%	4%	2%
Dysphagia	0%	0%	2%
Musculoskeletal			
Myalgia	3%	2%	6%
Arthralgia	1%	1%	4%
Arthritis	0%	0%	2%
Twitch	-	1%	2%
Nervous System			
Insomnia	6%	11%	16%
Dizziness	5%	7%	11%
Agitation	2%	3%	9%
Anxiety	3%	5%	6%
Tremor	1%	6%	3%
Nervousness	3%	5%	3%
Somnolence	2%	2%	3%
Irritability	2%	3%	2%
Memory decreased	1%	_	3%
Paresthesia	1%	1%	2%
Central nervous system stimulation	1%	2%	1%
Respiratory			
Pharyngitis	2%	3%	11%
Sinusitis	2%	3%	1%
Increased cough	1%	1%	2%
Skin	1/0	1/0	270
Sweating	2%	6%	5%
Rash	1%	5%	4%
Pruritus	2%	2%	4%
Urticaria	0%	2%	1%
Special Senses	U /0	L /0	1/0
•	20/	C9/	co/
Tinnitus	2%	6%	6%
Taste perversion	- 00/	2%	4%
Blurred vision or diplopia	2%	3%	2%
Urogenital	00/	00/	F0/
Urinary frequency	2%	2%	5%
Urinary urgency	0%	-	2%
Vaginal hemorrhage*	-	0%	2%
Urinary tract infection	_†	1%	0%

ncidence based on the number of female patients

 $^{\scriptscriptstyle \dagger}\textsc{Hyphen}$ denotes adverse reactions occurring in greater than 0 but less than 0.5% of patients. (300 to 600 mg per day) at an incidence of at least 1% more frequently than in the placebo group were; cardiac arrhythmia (5% vs. 4%), hypertension (4% vs. 2%), hypotension (3% vs. 2%), menstrual complaints (5% vs. 1%), akathisia (2% vs. 1%), impaired sleep quality (4% vs. 2%), sensory disturbance (4% vs. 3%), confusion (8% vs. 5%), decreased libido (3% vs. 2%), hostility (6% vs. 4%), auditory disturbance (5% vs. 3%), and gustatory disturbance (3% vs. 1%)

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

Table 4 summarizes the adverse reactions that occurred in patients treated with bupropion hydrochloric ded-release tablets (XL) for up to approximately 6 months in 3 placebo-controlled trials. These include reactions that occurred at an incidence of 2% or more and were more frequent than in the placebo group

Table 4: Adverse Reactions in Placebo-Controlled Trials in Patients with SAD

System Organ Class/Preferred Term

uctive System and Breast Disorder

Dysmenorrhea

r and Labyrinth Disorder

(n=511)Extended-Release Dry mouth Abdominal pain ous System Disorder Nasopharyngitis Upper respiratory tract infection Sinusitis chiatric Disorders Abnormal dreams Agitation loskeletal and Connective Tissue Disorder Feeling jittery Rash etabolism and Nutrition Disorder Decreased appetite

Hypertension **Table 5** presents the incidence of body weight changes (≥5 lbs) in the short-term MDD trials using bupropion HCI sustained-release. There was a dose-related decrease in body wei

Table 5: Incidence of Weight Gain or Weight Loss (≥5 lbs) in MDD Trials Using

Bupropion HCI Sustained-Release					
Weight Change	Bupropion HCI Sustained-Release 300 mg/day (n=339)	Bupropion HCI Sustained-Release 400 mg/day (n=112)	Placebo (n=347)		
ined >5 lbs	3%	2%	4%		
st >5 lbs	14%	19%	6%		

Table 6 presents the incidence of body weight changes (≥5 lbs) in the 3 SAD trials using bupropion HCl extended-release. A higher proportion of subjects in the bupropion group (23%) had a weight loss \geq 5 lbs, compared to the placebo group (11%). These were relatively long-term trials (up to 6 months

Table 6: Incidence of Weight Gain or Weight Loss (>5 lbs) in SAD Trials Using Bupropion HCI

	Extended-Release 150 to 300 mg/day (n=537)	(n=511)
Gained >5 lbs	11%	21%
Lost >5 lbs	23%	11%

size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug Chills, facial edema, edema, peripheral edema, musculoskeletal chest pain, photosensitivity, and malaise

n, hypertension, stroke, vasodilation, syncope, complete atrioventricular block, extrasystole Abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth

hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

MEDICATION GUIDE

buPROPion (bue-PROE-pee-on) Hydrochloride Extended-Release Tablets USP (XL)

IMPORTANT: Be sure to read the three sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with medicines used to guit smoking; and the third section is entitled "What Other Important Information Should I Know About Bupropion Hydrochloride Extended-Release Tablets

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines.

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

Antidepressant medicines may increase the risk of

suicidal thoughts or actions in some children, teenagers,

or young adults within the first few months of treatment. Depression or other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or

How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

• Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.

• Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.

as scheduled. Call the healthcare provider between

Keep all follow up visits with your healthcare provided

visits as needed, especially if you have concerns about symptoms. Call your healthcare provider right away if you or your family

member has any of the following symptoms, especially if they

- are new, worse, or worry you: thoughts about suicide or dying
- trouble sleeping (insomnia) attempts to commit suicide

new or worse depression

new or worse irritability

panic attacks

- acting aggressive, being angry, or violent
- new or worse anxiety acting on dangerous impulses
- feeling very agitated or restless an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood
- Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant

What else do I need to know about antidepressant medicines?

- medicine suddenly can cause other symptoms. Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just
- the use of antidepressants. **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member
- Antidepressant medicines can interact with other **medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

t is not known if bupropion hydrochloride extended-release tablets (XL) are safe and effective in children under the age

Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or

This section of the Medication Guide is only about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with drugs used to quit smoking. Although bupropion hydrochloride extended-release tablets (XL) are not a treatment for quitting smoking, it contains the same active ingredient (bupropion hydrochloride) as ZYBAN® which is used | to help patients quit smoking.

Talk to your healthcare provider or your family member's healthcare provider about:

all risks and benefits of quit-smoking medicines.

 all treatment choices for quitting smoking. When you try to quit smoking, with or without bupropion you may have symptoms that may be due to nicotine withdrawal,

 urge to smoke frustration

including:

- restlessness depressed mood
- anger
- decreased heart rate trouble sleeping feeling anxious
- increased appetite

irritability

 difficulty concentrating weight gain

Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

Some people have had serious side effects while taking bupropion to help them quit smoking, including:

New or worse mental health problems, such as changes

in behavior or thinking, aggression, hostility, agitation, depression, or suicidal thoughts or actions. Some people had these symptoms when they began taking bupropion, and others developed them after several weeks of treatment, or after stopping bupropion. These symptoms happened more often in people who had a history of mental health problems before taking bupropion than in people without a history of mental health problems.

Stop taking bupropion hydrochloride extended-release tablets (XL) and call your healthcare provider right away if you, your family, or caregiver notice any of these symptoms. Work with your healthcare provider to decide whether you should continue to take bupropion hydrochloride extended-release tablets (XL). In many people, these symptoms went away after stopping bupropion hydrochloride extended-release tablets (XL), but in some people symptoms continued after stopping bupropion hydrochloride extended-release tablets (XL). It is important for you to follow-up with your healthcare provider until your symptoms go away. Before taking bupropion hydrochloride extended-release tablets (XL), tell your healthcare provider if you have ever had depression or other mental health problems. You should also tell your healthcare provider about any symptoms you had during other times you tried to quit smoking, with or without bupropion

What Other Important Information Should I Know About Bupropion Hydrochloride Extended-Release Tablets (XL)?

Seizures: There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets (XL), especially in people:

 with certain medical problems. who take certain medicines.

The chance of having seizures increases with higher doses of bupropion hydrochloride extended-release tablets (XL). For more information, see the sections "Who should not take bupropion hydrochloride extended-release tablets (XL)?" and "What should I tell my healthcare provider before taking bupropion hydrochloride extended-release tablets (XL)?" Tell your healthcare provider about all of your medical conditions and all the medicines you take. Do not take any other medicines while you are taking bupropion hydrochloride extended-release tablets (XL) unless your healthcare provider has said it is okay to take them.

If you have a seizure while taking bupropion hydrochloride extended-release tablets (XL), stop taking the tablets and call your healthcare provider right away. Do not take bupropion hydrochloride extended-release tablets (XL) again if you have a seizure.

 High blood pressure (hypertension). Some people get high blood pressure that can be severe, while taking bupropion hydrochloride extended-release tablets (XL). The chance of high blood pressure may be higher if you also use nicotine replacement therapy (such as a nicotine patch) to help you stop smoking (see the section of this Medication Guide called "How should I take bupropion hydrochloride extended-release tablets (XL)?").

Manic episodes. Some people may have periods of mania while taking bupropion hydrochloride extended-release tablets (XL), including:

- Greatly increased energy Severe trouble sleeping
- Racing thoughts Reckless behavior

Unusually grand ideas

 Excessive happiness or irritability Talking more or faster than usual

If you have any of the above symptoms of mania, call your

- healthcare provider. **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while taking bupropion hydrochloride extended-release tablets (XL), including delusions (believe you are someone else), hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are against you), or feeling confused. If this happens to you, call
- Visual Problems.

eve pain

changes in vision swelling or redness in or around the eye

your healthcare provider.

Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

 Severe allergic reactions. Some people can have severe allergic reactions to bupropion hydrochloride extendedrelease tablets (XL). Stop taking bupropion hydrochloride extended-release tablets (XL) and call your healthcare **provider right away** if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious allergic

What are Bupropion Hydrochloride Extended-Release Tablets

Bupropion hydrochloride extended-release tablets (XL) should be used with a patient support program. It is important to participate in the behavioral program, counseling, or other

support program your healthcare professional recommends. Quitting smoking can lower your chances of having lung disease, heart disease, or getting certain types of cancer that

Who should not take bupropion hydrochloride extendedrelease tablets (XL)?

Do not take bupropion hydrochloride extended-release

have or had a seizure disorder or epilepsy.

are related to smoking.

tablets (XL) if you:

have or had an eating disorder such as anorexia nervosa or

are taking any other medicines that contain bupropion. including WELLBUTRIN (bupropion hydrochloride tablets), WELLBUTRIN SR (bupropion hydrochloride extendedrelease tablets (SR)), APLENZIN®, ZYBAN, or FORFIVO XL®. Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).

drink a lot of alcohol and abruptly stop drinking, or take

healthcare provider or pharmacist if you are not sure if you

medicines called sedatives (these make you sleepy), benzodiazepines, or anti-seizure medicines, and you stop taking them all of a sudden. take a monoamine oxidase inhibitor (MAOI). Ask your

take an MAOI, including the antibiotic linezolid.

do not take an MAOI within 2 weeks of stopping bupropion hydrochloride extended-release tablets (XL) unless directed to do so by your healthcare provider. do not start bupropion hydrochloride extended-release

tablets (XL) if you stopped taking an MAOI in the last

2 weeks unless directed to do so by your healthcare

are allergic to the active ingredient in bupropion hydrochloride extended-release tablets (XL), bupropion, or to any of the inactive ingredients. See the end of this Medication Guide for a complete list of ingredients in bupropion hydrochloride extended-release tablets (XL)

bupropion hydrochloride extended-release tablets (XL)? Tell your healthcare provider if you have ever had depression suicidal thoughts or actions, or other mental health problems

You should also tell your healthcare provider about any symptoms

you had during other times you tried to quit smoking, with or

What should I tell my healthcare provider before taking

without bupropion hydrochloride extended-release tablets (XL). See "Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Tell your healthcare provider about your other medical

 have liver problems, especially cirrhosis of the liver. have kidney problems.

have, or have had, an eating disorder such as anorexia nervosa or bulimia. have had a head injury.

conditions, including if you:

have had a seizure (convulsion, fit). have a tumor in your nervous system (brain or spine).

have had a heart attack, heart problems, or high blood

 are a diabetic taking insulin or other medicines to control your blood sugar.

extended-release tablets (XL).

tablets (XL).

drink alcohol.

 abuse prescription medicines or street drugs. are pregnant or plan to become pregnant. are breastfeeding. Bupropion passes into your milk in

small amounts. Tell your healthcare provider about all the medicines you take, including prescription, over-the-counter medicines, vitamins, and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are taking bupropion hydrochloride

How should I take bupropion hydrochloride extended-release

Start bupropion hydrochloride extended-release tablets (XL)

before you stop smoking to give bupropion hydrochloride

extended-release tablets (XL) time to build up in your body. It takes about 1 week for bupropion hydrochloride extendedrelease tablets (XL) to start working. Pick a date to stop smoking that is during the second week you are taking bupropion hydrochloride extended-release

Take bupropion hydrochloride extended-release tablets (XL) exactly as prescribed by your healthcare provider. Do not change your dose or stop taking bupropion hydrochloride extended-release tablets (XL) without talking with your healthcare provider first.

Bupropion hydrochloride extended-release tablets (XL) are usually taken for 7 to 12 weeks. Your healthcare provider may decide to prescribe bupropion hydrochloride extendedrelease tablets (XL) for longer than 12 weeks to help you stop smoking. Follow your healthcare provider's instructions. Swallow bupropion hydrochloride extended-release

tablets (XL) whole. Do not chew, cut, or crush bupropion **hydrochloride extended-release tablets (XL).** If you do, the medicine will be released into your body too quickly. If this happens you may be more likely to get side effects including seizures. Tell your healthcare provider if you cannot swallow tablets.

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- Bupropion hydrochloride extended-release tablets (XL) may have an odor. This is normal.
- Take your doses of bupropion hydrochloride extended-release tablets (XL) at least 8 hours apart.
- You may take bupropion hydrochloride extended-release tablets (XL) with or without food.
- It is not dangerous to smoke and take bupropion hydrochloride extended-release tablets (XL) at the same time. But, you will lower your chance of breaking your smoking habit if you smoke after the date you set to stop smoking.
- You may use bupropion hydrochloride extended-release tablets (XL) and nicotine patches (a type of nicotine replacement therapy) at the same time, following the precautions below.
- You should only use bupropion hydrochloride extendedrelease tablets (XL) and nicotine patches together under the care of your healthcare provider. Using bupropion hydrochloride extended-release tablets (XL) and nicotine patches together may raise your blood pressure, and sometimes this can be severe.
- Tell your healthcare provider if you plan to use nicotine patches. Your healthcare provider should check your blood pressure regularly if you use nicotine patches with bupropion hydrochloride extended-release tablets (XL) to help you quit smoking.
- If you miss a dose, do not take an extra dose to make up for the dose you missed. Wait and take your next dose at the regular time. **This is very important**. Too much bupropion hydrochloride extended-release tablets (XL) can increase your chance of having a seizure.
- If you take too much bupropion hydrochloride extendedrelease tablets (XL), or overdose, call your local emergency room or poison control center right away.

Do not take any other medicines while taking bupropion hydrochloride extended-release tablets (XL) unless your healthcare provider has told you it is okay.

What should I avoid while taking bupropion hydrochloride extended-release tablets (XL)?

- Limit or avoid using alcohol during treatment with bupropion hydrochloride extended-release tablets (XL). If you usually drink a lot of alcohol, talk with your healthcare provider before suddenly stopping. If you suddenly stop drinking alcohol, you may increase your chance of having seizures.
- Do not drive a car or use heavy machinery until you know how bupropion hydrochloride extended-release tablets (XL) affect you. Bupropion hydrochloride extended-release tablets (XL) can affect your ability to do these things safely.

What are possible side effects of bupropion hydrochloride extended-release tablets (XL)?

Bupropion hydrochloride extended-release tablets (XL) can cause serious side effects. See the sections at the beginning of this Medication Guide for information about serious side effects of bupropion hydrochloride extended-release tablets (XL).

The most common side effects of bupropion hydrochloride extended-release tablets (XL) include:

- trouble sleeping
- feeling anxious
- stuffy nose nausea
- dry mouth constipation
- dizziness
- ioint aches

If you have trouble sleeping, do not take bupropion hydrochloride extended-release tablets (XL) too close to bedtime.

Tell your healthcare provider right away about any side effects

These are not all the possible side effects of bupropion hydrochloride extended-release tablets (XL). For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to TWi Pharmaceuticals, Inc. at 1-844-518-2989.

How should I store bupropion hydrochloride extendedrelease tablets (XL)?

- Store bupropion hydrochloride extended-release tablets (XL) at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature1.
- Protect from light.

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Keep bupropion hydrochloride extended-release tablets (XL) and all medicines out of the reach of children.

General information about the safe and effective use of bupropion hydrochloride extended-release tablets (XL).

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use bupropion hydrochloride extended-release tablets (XL) for a condition for which it was not prescribed. Do not give bupropion hydrochloride extended-release tablets (XL) to other people, even if they have the same symptoms you have. It may harm them.

If you take a urine drug screening test, bupropion hydrochloride extended-release tablets (XL) may make the test result positive for amphetamines. If you tell the person giving you the drug screening test that you are taking bupropion hydrochloride extended-release tablets (XL), they can do a more specific drug screening test that should not have this problem.

This Medication Guide summarizes important information about bupropion hydrochloride extended-release tablets (XL). If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about bupropion hydrochloride extended-release tablets (XL) that is written for health professionals.

For more information about bupropion hydrochloride extendedrelease tablets (XL), go to www.twipharma.com or call 1-844-518-2989

What are the ingredients in bupropion hydrochloride extended-release tablets (XL)?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: hypromellose, glyceryl behenate, hydroxypropyl cellulose, colloidal silicon dioxide, ethylcellulose, povidone, methacrylic acid copolymer type C, triethyl citrate, iron oxide black and propylene glycol. The tablets are printed with edible black ink.

Manufactured for:

TWi Pharmaceuticals USA, Inc. Paramus, NJ 07652

Manufactured by:

TWi Pharmaceuticals, Inc. Taoyuan City, 32063, Taiwan

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 01/2019

Hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone secretion.

Hemic and Lymphatic leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered 9.2 Abuse PT and/or INR, associated with hemorrhagic or thrombotic complications, were observed when bupropion was

coadministered with warfarin. Metabolic and Nutritional

<u>Musculoskeletal</u> eg cramps, fever/rhabdomyolysis, and muscle weakness.

Nervous System

Abnormal coordination, depersonalization, emotional lability, hyperkinesia, hypertonia, hypesthesia, vertigo, amnesia, ataxia, derealization, abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma. dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hypokinesia, increased libido, neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive dyskinesia.

Respiratory

Maculopapular rash, alopecia, angioedema, exfoliative dermatitis, and hirsutism. Special Senses ormality, dry eye, deafness, increased intraocular pressure, angle-closure glaucoma, and

mydriasis.

Urogenital ence, polyuria, prostate disorder, abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia,

menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

Potential for Other Drugs to Affect Bupropion Hydrochloride Extended-Release Tablets (XL) Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between bupropion hydrochloride extended-release tablets (XL) and drugs that are inhibitors or inducers of CYP2B6

Inhibitors of CYP2B6 Ticlopidine and Clopidogrel: Concomitant treatment with these drugs can increase bupropion exposures but decrease hydroxybupropion exposure. Based on clinical response, dosage adjustment of bupropion hydrochloride extended-release tablets (XL) may be necessary when coadministered with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) [see Clinical Pharmacology (12.3)].

Ritonavir, Lopinavir, and Efavirenz: Concomitant treatment with these drugs can decrease bupropion and hydroxybupropion exposure. Dosage increase of bupropion hydrochloride extended-release tablets (XL) may nistered with ritonavir, lopinavir, or efavirenz but should not exceed the maximum

recommended dose [see Clinical Pharmacology (12.3)]. Carbamazepine, Phenobarbital, Phenytoin: While not systemically studied, these drugs may induce metabolism

recommended dose should not be exceeded.

7.2 Potential for Bupropion Hydrochloride Extended-Release Tablets (XL) to Affect Other Drugs **Drugs Metabolized by CYP2D6**

Bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. Therefore, coadministration of bupropion hydrochloride extended-release tablets (XL) with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. Such drugs include certain antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, and sertraline), antipsychotics (e.g., haloperidol, risperidone, and thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, and flecainide). When used concomitantly with bupropion hydrochloride extended-release tablets (XL), it may be necessary to decrease the dose of these CYP2D6 substrates, particularly for drugs with a narrow therapeutic index

Drugs that require metabolic activation by CYP2D6 to be effective (e.g., tamoxifen), theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Patients treated concomitantly with bupropion hydrochloride extended-release tablets (XL) and such drugs may require increased doses of the drug [see Clinical Pharmacology (12.3)]. 7.3 Drugs That Lower Seizure Threshold

Use extreme caution when coadministering bupropion hydrochloride extended-release tablets (XL) with other drugs that lower the seizure threshold (e.g., other bupropion products, antipsychotics, antidepressants, theophylline, or systemic corticosteroids). Use low initial doses of bupropion hydrochloride extended-release tablets (XL) and increase the dose gradually [see Warnings and Precautions (5.3)].

7.4 Dopaminergic Drugs (Levodopa and Amantadine)
Bupropion, levodopa, and amantadine have dopamine agonist effects. CNS toxicity has been reported when buppopion was coadministered with levodopa or amantadine. Adverse reactions have included restlessness. agitation, tremor, ataxia, gait disturbance, vertigo, and disziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Use caution when administering bupropion hydrochloride extendedrelease tablets (XL) concomitantly with these drugs.

7.5 Use with Alcohol In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion hydrochloride extended-release tablets (XL). The consumption of alcohol during treatment with bupropion hydrochloride extended-release

7.6 MAO Inhibitors Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of MAOIs and bupropion is ated because there is an increased risk of hypertensive reactions if bupropion is used cond with MAOIs. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. At least 14 days should elapse between discontinuation of an MAOI intended to treat pression and initiation of treatment with bupropion hydrochloride extended-release tablets (XL). Conversely, at least 14 days should be allowed after stopping bupropion hydrochloride extended-release tablets (XL) before starting an MAOI antidepressant [see Dosage and Administration (2.8, 2.9) and Contraindications (4)].

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

8 USE IN SPECIFIC POPULATIONS

Pregnancy Category C

Data from epidemiological studies including pregnant women exposed to bupropion in the first trimester indicate no increased risk of congenital malformations overall. All pregnancies regardless of drug exposure have a background rate of 2% to 4% for major malformations and 15% to 20% for pregnancy loss. No clear evidence of teratogenic activity was found in reproductive developmental studies conducted in rats and rabbits. However, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at doses approximately equal to the maximum recommended human dose (MRHD) and greater and decreased fetal weights were seen at doses twice the MRHD and greater. Bupropion hydrochloride extended-release tablets (XL) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

ata from an international bupropion Pregnancy Registry (675 first trimester exposures) and a retrospective cohort study using the United Healthcare database (1,213 first trimester exposures) did not show an increased

No increased risk for cardiovascular malformations overall has been observed after bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester from the international Pregnancy Registry was 1.3% (9 background rate of cardiovascular malformations (approximately 1%). Data from the United Healthcare database and a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 with a case-controlled study (6,853 infants with cardiovascular malformations and 5,753 wi non-cardiovascular malformations) from the National Birth Defects Prevention Study (NBDPS) did not show erythrohydrobupropion and threehlydrobupropion metabolites are similar to that of hydroxybupropion. However, an increased risk for cardiovascular malformations overall after bupropion exposure during the first trimester.

Study findings on bupropion exposure during the first trimester and risk left ventricular outflow tract obstruction

the elimination half-lives of erythrohydrobupropion and threohydrobupropion are longer, approximately 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs were 1.4 and 7 times that of bupropion, respectively. (VOTO) are inconsistent and do not allow conclusions regarding possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted OR = 2.6; 95% Cl 1.2, 5.7) and the Slone Epidemiology case control study did not find increased

Study findings on bupropion exposure during the first trimester and risk for ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n= 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0) but did not find an increased risk for any other cardiovascular malformations studied (including LVOTO as above). The NBDPS and United Healthcare database study did not find an association between first

For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control

In studies conducted in rats and rabbits, bupropion was administered orally at doses of up to 450 and 150. mg/kg/day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg/m² basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m² basis) and greater. Decreased fetal veights were observed at 50 mg/kg and greater. When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m² basis) prior to mating and throughout pregnancy

and lactation, there were no apparent adverse effects on offspring development 8.3 Nursing Mothers Bupropion and its metabolites are present in human milk. In a lactation study of ten women, levels of orally dosed bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure suming 150 mL/kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Exercise caution when bupropion hydrochloride extended-release tablets (XL) are

administered to a nursing woman. 8.4 Pediatric Use Safety and effectiveness in the pediatric population have not been established. When considering the use of bupropion hydrochloride extended-release tablets (XL) in a child or adolescent, balance the potential risks with

the clinical need [see Boxed Warning and Warnings and Precautions (5.1)]. 8.5 Geriatric Use Of the approximately 6000 patients who participated in clinical trials with bupropion hydrochloride sustained release tablets (depression and smoking cessation studies). 275 were ≥65 years old and 47 were ≥75 years told. In addition, several hundred patients 2-65 years of age participated in clinical trials using the immediate-release formulation of bupropion hydrochloride (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Reported clinical experience has

ot identified differences in responses between the elderly and younger patients, but greater sensitivity of some

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be necessary to consider this factor in dose selection; it may be useful to monitor renal function [see Dosage and Administration (2.7), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]. 8.6 Renal Impairment

older individuals cannot be ruled out.

Administration (2.6) and Clinical Pharmacology (12.3)].

Consider a reduced dose and/or dosing frequency of bupropion hydrochloride extended-release tablets (XL) in patients with renal impairment (glomerular filtration rate: <90 mL/min). Bupropion and its metabolites are cleared renally and may accumulate in such patients to a greater extent than usual. Monitor closely for adverse reactions that could indicate high bupropion or metabolite exposures [see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]. 8.7 Hepatic Impairment

In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum bupropion hydrochloride extended-release tablets (XL) dose is 150 mg every other day. In patients with mild hepatic ment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing [see Dosage and

DRIIG ARIISE AND DEPENDENCE

Controlled Substance Bupropion is not a controlled substance

Controlled clinical studies of bupropion HCl immediate-release conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients demonstrated an increase in motor activity

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg bupropion produce

mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), and a score intermediate between placebo and amphetamine on the Liking healthy male and female volunteers: 17 were chronic cigarette smokers and 17 were nonsmokers. Following Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability. oral administration of a single 150 mg dose of bupropion, there was no statistically significant difference in Findings in clinical trials, however, are not known to reliably predict the abuse notential of drugs. Nonetheless C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be significantly reinforcing to amphetamine or CNS stimulant **Drug Interactions** abusers. However, higher doses (that could not be tested because of the risk of seizure) might be modestly

Bupropion hydrochloride extended-release tablets are intended for oral use only. The inhalation of crushe drugs that are inhibitors or inducers of CYP2B6. In addition, *in vitro* studies suggest that paroxetine, sertraline, tablets or injection of dissolved bupropion has been reported. Seizures and/or cases of death have been reported norfluoxetine, fluvoxamine, and nelfinavir inhibit the hydroxylation of bupropion when bupropion has been administered intranasally or by parenteral injection Ticlopidine and Clopidogrel: In a study in healthy male volunteers, clopidogrel 75 mg once daily or ticlopidine

Studies in rodents and primates demonstrated that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models assessing the positive reinforcing effects of psychoactive drugs, bupropion was selfadministered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative timulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive

10.1 Human Overdose Experience

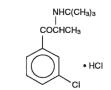
verdoses of up to 30 grams or more of bupropion have been reported. Seizure was reported in approximately one nird of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have peen reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac

10.2 Overdosage Management Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified

poison control centers are listed in the Physicians' Desk Reference (PDR). Call 1-800-222-1222 or refer to www.poison.org. of bupropion and may decrease bupropion exposure [see Clinical Pharmacology (12.3)]. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum metabolism of bupropion.

in hydrochloride extended-release tablets USP (XL), an antidepressant of the aminoketone class, are chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitor, or other known intidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenyle It is designated as $(\pm)-1-(3$ -chorophenyl)-2-[(1,1dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is C₁₃H₁₈CINO•HCl. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a hitter taste and produces the sensation of local anesthesia on



ropion hydrochloride extended-release tablets USP (XL) are supplied for oral administration as 150 mg 13 and 300 mg white film coated extended-release tablets. Each tablet contains the labeled amount of bupropion loride and the inactive ingredients: hypromellose, glyceryl behenate, hydroxypropyl cellulose, co silicon dioxide, ethylcellulose, povidone, methacrylic acid copolymer type C, triethyl citrate, iron oxide black and propylene glycol. The tablets are printed with edible black ink.

The insoluble shell of the extended-release tablet may remain intact during gastrointestinal transit and is Meets USP Dissolution Test 8

12.1 Mechanism of Action

The mechanism of action of bupropion is unknown, as is the case with other antidepressants. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine and does not inhibit

Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers

have not been studied. Following chronic dosing, the mean steady-state plasma concentration of bupropion was reached within 8 days. The mean elimination half-life (\pm SD) of bupropion is 21 (\pm 9) hours.

with doses of 300 mg to 450 mg per day. The trial demonstrated the efficacy of bupropion as measured by the Hamilton Depression Rating Scale (HAMD) total score, the HAMD depressed mood item (item 1), and the Clinical In a study comparing 14-day dosing with bupropion hydrochloride extended-release tablets (XL), 300 mg once-daily to the immediate-release formulation of bupropion at 100 mg 3 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the three metabolites Global Impressions-Severity Scale (CGI-S). The second study included 2 fixed doses of bupropion (300 mg and 450 mg per day) and placebo. This trial demonstrated the efficacy of bupropion for only the 450 mg dose. The efficacy results were significant for the HAMD total score and the CGI-S severity score, but not for HAMD item 1. (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion). Additionally, in a study comparing 14day dosing with bupropion hydrochloride extended-release tablets (XL) 300 mg once daily to the sustain In the third study, outpatients were treated with bupropion 300 mg per day. This study demonstrated the efficacy release formulation of bupropion at 150 mg 2 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the three metabolites.

ollowing single oral administration of bupropion hydrochloride extended-release tablets (XL) to healthy volunteers, the median time to peak plasma concentrations for bupropion was approximately 5 hours. The presence of food did not affect the peak concentration or area under the curve of bupropion.

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

Rupropion is extensively metabolized in humans. Three metabolites are active, hydroxyhupropion, which is formed hydroxylation of the *tert*-butyl group of bupropion, and the amino-alcohol isomers threohydrobuprop and erythrohydrobupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 enzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than

bupropion. This may be of clinical importance, because the plasma concentrations of the metabolites are as (fourth week of March), resulting in a treatment duration of approximately 4 to 6 months for the majority of patients. Patients were randomized to treatment with bupropion hydrochloride extended-release tablets (XL) or placebo. The initial bupropion dose was 150 mg once daily for 1 week, followed by up-titration to 300 mg once administration of bupropion hydrochloride extended-release tablets (XL), and it was approximately 7 times 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 doses in the 3 trial 26% continued for <3 months, 15% continued for >6 months. To enter the trials, patients must have had a low level of depressive symptoms, as demonstrated by a score of

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg/day. lowing oral administration of 200 mg of ¹⁴C-bupropion in humans, 87% and 10% of the radioactive dose

specifically assessing core symptoms of seasonal affective disorder: social withdrawal, weight gain, increased were recovered in the urine and feces, respectively. Only 0.5% of the oral dose was excreted as unchanged appetite, increased eating, carbohydrate craving, hypersomnia, and fatigability. The primary efficacy endpoir was the onset of a seasonal major depressive episode. The criteria for defining an episode included: 1) the for depressive symptoms, or 2) a SIGH-SAD score of >20 on 2 consecutive weeks. The primary analysis was a

actors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure [CHF], 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.

ere is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-trial comparison between normal subjects and subjects with end-stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3-and 2.8-fold increase, respectively, in AUC for subjects with endstage renal failure. A second study, comparing normal subjects and subjects with moderate-to-severe renal 24979-101-02). impairment (GFR 30.9 ± 10.8 mL/min) showed that after a single 150 mg dose of sustained-release bupropion, exposure to bupropion was approximately 2-fold higher in subjects with impaired renal function, while levels of the hydroxybupropion and threo/erythrohydrobupropion (combined) metabolites were similar in the 2 groups. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. The elimination of the major metabolites of bupropion may be reduced by impaired renal function. Bupropion hydrochloride extended-release tablets (XL) should be used with caution in natients with renal imnairment, and a reduced frequency and/or dose should be considered [see Dosage and

The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose 17 PATIENT COUNSELING INFORMATION trials, one in subjects with alcoholic liver disease and one in subjects with mild to severe cirrhosis. The first trial demonstrated that the half-life of hydroxybupropion was significantly longer in 8 subjects with alcoholic liver liver to the half-life of hydroxybupropion was significantly longer in 8 subjects with alcoholic liver liver the patient to read the FDA-approved patient labeling (Medication Guide). Inform patients, their families, and their caregivers about the benefits and risks associated with treatment with disease than in 8 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 groups were minimal

The second trial demonstrated no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 subjects with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, Cmax, and T_{max}) and its active metabolites ($t_{1/2}$) in subjects with mild to moderate hepatic cirrhosis. In addition in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy olunteers; the mean bupropion half-life was also longer (29 hours in subjects with severe hepatic cirrhosis s. 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythrohydrobupropion. The median $T_{\rm max}$ was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/ pion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosi compared to healthy volunteers [see Dosage and Administration (2.6) and Use in Specific Populations (8.7)]. Left Ventricular Dysfunction

During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), there was no apparent effect on the pharmacokinetics of bupropion or its netabolites, compared to healthy volunteers.

e 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 3 times daily schedule, revealed no relationship strated that the disposition of bupropion and its metabolites in elderly subjects was similar to that in

younger subjects. These data suggest that there is no prominent effect of age on bupropion concentration; however, another single-and multiple-dose pharmacokinetic study suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see Use in Specific Populations (8.5)).

approximately 13% higher in male volunteers compared to female volunteers.

Potential for Other Drugs to Affect Runronion Hydrochloride Extended-Release Tablets (XL)

Prasugrel: In healthy subjects, prasugrel increased bupropion C_{max} and AUC values by 14% and 18%.

healthy young male volunteers, the pharmacokinetics of bupropion and hydroxybupropion were unaffected

by 23%, the threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%. In

a second healthy volunteer study, ritonavir 600 mg twice daily decreased the AUC and C_{max} of bupropion by 66% and 62%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 78%, the

In another healthy volunteer study, lopinavir 400 mg/ritonavir 100 mg twice daily decreased bupropion AUC and

Efavirenz: In a study of healthy volunteers, efavirenz 600 mg once daily for 2 weeks reduced the AUC and C_{max} of

hunronion by approximately 55% and 34%, respectively. The AUC of hydroxybupropion was unchanged, wherea

Carbamazepine, Phenobarbital, Phenytoin: While not systematically studied, these drugs may induce the

nimal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In a study

vas no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically

of 8 healthy male volunteers, following a 14-day administration of bupropion 100 mg three times per day, there

Citalogram: Although citalogram is not primarily metabolized by CYP2D6, in one study bupropion increased the

Lamotrigine: Multiple oral doses of bupropion had no statistically significant effects on the single-dose

human dose (MRHD), respectively, on a mg/m² basis. In the rat study there was an increase in nodula

o 7 times the MRHD on a mg/m² basis); lower doses were not tested. The question of whether or not such

lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in one Ames

bacterial mutagenicity assay, but was negative in another. Bupropion produced an increase in chromosoma

The efficacy of bupropion in the treatment of major depressive disorder was established with the immediate

dose range was 300 mg to 600 mg per day administered in 3 divided doses; 78% of patients were treated

f bupropion as measured by the HAMD total score, the HAMD item 1, the Montgomery-Asberg Depression Rating

A longer-term, placebo-controlled, randomized withdrawal trial demonstrated the efficacy of bupropion HCl

sustained-release in the maintenance treatment of MDD. The trial included adult outpatients meeting DSM-IV

criteria for MDD, recurrent type, who had responded during an 8-week open-label trial of bupropion 300 mg per day. Responders were randomized to continuation of bupropion 300 mg per day or placebo for up to 44 weeks of

phase was defined as the investigator's judgment that drug treatment was needed for worsening depressive

symptoms. Patients in the bupropion group experienced significantly lower relapse rates over the subsequent

Although there are no independent trials demonstrating the efficacy of bupropion hydrochloride extended

release tablets (XL) in the acute treatment of MDD, studies have demonstrated similar bioavailability between

The efficacy of bupropion hydrochloride extended-release tablets (XL) in the prevention of seasonal major

trials in adult outpatients with a history of MDD with an autumn-winter seasonal pattern (as defined by DSM-

IV criteria). Bupropion treatment was initiated prior to the onset of symptoms in the autumn (September to

November). Treatment was discontinued following a 2 week taper that began during the first week of spring

ranged from 257 mg to 280 mg per day. Approximately 59% of patients continued in the study for 3 to 6 months;

7 on the Hamilton Depression Rating Scale-17 (HAMD17) and a HAMD24 score of <14. The primary efficacy

measure was the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective

Disorders (SIGH-SAD), which is identical to the HAMD24. The SIGH-SAD consists of the HAMD17 plus 7 items

In these 3 trials, the percentage of patients who were depression-free (did not have an episode of MDD) at the

end of treatment was significantly higher in the bupropion group than in the placebo group: 81.4% vs. 69.7%,

Bupropion hydrochloride extended-release tablets USP (XL), 150 mg of bupropion hydrochloride, are round, white film coated tablets printed with "T101" in black ink on one side and plain on the other side and are

available in bottles of 30 tablets (NDC 24979-101-06), 90 tablets (NDC 24979-101-07) and 500 tablets (NDC

Rupropion hydrochloride extended-release tablets IISP (XI) 300 mg of hupropion hydrochloride are round

white film coated tablets printed with "T102" in black ink on one side and plain on the other side and are available in bottles of 30 tablets (NDC 24979-102-06), 90 tablets (NDC 24979-102-07) and 500 tablets (NDC

87.2% vs. 78.7%, and 84.0% vs. 69.0% for Trials 1, 2 and 3, respectively. For the 3 trials combined, the sion-free rate was 84.3% versus 72.0% in the bupropion and placebo group, respectively.

comparison of depression-free rates between the bupropion and placebo groups.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

bupropion hydrochloride extended-release tablets (XL) and counsel them in its appropriate use.

A patient Medication Guide about "Antidepressant Medicines, Depression and Other Serious Mental Illnesses

and Suicidal Thoughts or Actions," "Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions," and "What Other Important Information Should I

Know About bupropion hydrochloride extended-release tablets (XL)?" is available for bupropion hydrochloride

extended-release tablets (XL). Instruct patients, their families, and their caregivers to read the Medication Guide and assist them in understanding its contents. Patients should be given the opportunity to discuss the

contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of

Advise patients regarding the following issues and to alert their prescriber if these occur while taking bupropior

hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation,

especially early during antidepressant treatment and when the dose is adjusted up or down. Advise families and caregivers of patients to observe for the emergence of such symptoms on a day-to-day basis, since changes

may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially

if they are sewere, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very

Although burpopion hydrochloride extended-release tablets (XL) are not indicated for smoking cessation treatment, it contains the same active ingredient as ZYBAN® which is approved for this use. Inform patients that

some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal

ideation and suicide when attempting to quit smoking while taking bupropion. Instruct patients to discontinu

Instruct patients, their families, and/or their caregivers to be aiert to the emergence or anxiety, agriation attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restless).

Neuropsychiatric Adverse Events and Suicide Risk in Smoking Cessation Treatment

, and/or their caregivers to be alert to the emergence of anxiety, agitation, panic

Bupropion hydrochloride extended-release tablets (XL) may have an odor.

the Medication Guide is reprinted at the end of this document.

close monitoring and possibly changes in the medication.

hydrochloride extended-release tablets (XL)

Suicidal Thoughts and Behaviors

HOW SUPPLIED/STORAGE AND HANDLING

24979-102-02)

Protect from light.

depressive episodes associated with SAD was established in 3 randomized, double-blind, placebo-co

the immediate-, sustained-, and extended-release formulations of bupropion HCI under steady-state conditio (i.e., the exposures $[C_{max}$ and AUC] for bupropion and its metabolites are similar among the 3 formulations).

servation for relapse. Response during the open-label phase was defined as a CGI-Improvement Scale score

(very much improved) or 2 (much improved) for each of the final 3 weeks. Relapse during the double-blind

Scale (MADRS), the CGI-S score, and the CGI-Improvement Scale (CGI-I) score.

44 weeks compared to those in the placebo group.

14.2 Seasonal Affective Disorder

elease formulation of bupropion hydrochloride in two 4-week, placebo-controlled trials in adult inpatients with IDD and in one 6-week, placebo-controlled trial in adult outpatients with MDD. In the first study, the bupropion

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

in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study

arcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day hydrochloride, respectively. These doses are approximately 7 and 2 times the maximum recommended

Citalopram: Citalopram did not affect the pharmacokinetics of bupropion and its three metabolites.

threohydrobupropion decreased by 50%, and the erythrohydrobupropion decreased by 68%.

Potential for Bunropion Hydrochloride Extended-Release Tablets (XL) to Affect Other Drugs

mportant alterations of blood levels of coadministered drugs.

C_{max} and AUC of citalogram by 30% and 40%, respectively

pharmacokinetics of lamotrigine in 12 healthy volunteers.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.

14 CLINICAL STUDIES

Inducers of CYP2B6

tively, and decreased C_{max} and AUC values of hydroxybupropion by 32% and 24%, respectively.

A single-dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex-related differences in the pharmacokinetic parameters of bupropion. In addition, pooled analysis of bupropion pharmacokinetic data from 90 healthy male and 90 healthy female volunteers revealed no sex-related differences in the peak plasma concentrations of bupropion. The mean systemic exposure (AUC) was

Educate patients on the symptoms of hypersensitivity and to discontinue bupropion hydrochloride extended-release tablets (XL) if they have a severe allergic reaction.

Instruct patients to discontinue and not restart bupropion hydrochloride extended-release tablets (XL) if they experience a seizure while on treatment. Advise patients that the excessive use or the abrupt disconti of alcohol, benzodiazepines, antiepileptic drugs, or sedatives/hypnotics can increase the risk of seizure. Advise

patients to minimize or avoid the use of alcoho Angle-Closure Glaucoma

 ${\it In vitro} \ {\it studies} \ indicate \ that \ bupropion \ is \ primarily \ metabolized \ to \ hydroxybupropion \ by \ CYP2B6. \ Therefore, the potential exists for drug interactions between bupropion hydrochloride extended-release tablets (XL) and the potential exists of the potential exists for drug interactions between bupropion hydrochloride extended-release tablets (XL) and the potential exists for drug interactions between bupropion hydrochloride extended-release tablets (XL) and the potential exists for drug interactions between bupropion hydroxybupropion by the potential exists for drug interactions between bupropion hydroxybupropion by the potential exists for drug interactions between bupropion hydroxybupropion by the potential exists for drug interactions between bupropion hydroxybupropion by the potential exists for drug interactions between bupropion hydroxybupropion by the potential exists for drug interactions between bupropion hydroxybupropion by the potential exists for drug interactions between bupropion hydroxybupropion by the potential exists for drug interactions between bupropion hydroxybupropion by the potential exists for drug interactions between bupropion hydroxybupropion by the potential exists for drug interactions and the potential exists for th$ have a prophylactic procedure (e.g., iridectomy), if they are susceptible [see Warnings and Precautions (5.7)] **Bupropion-Containing Products** Educate patients that bupropion hydrochloride extended-release tablets (XL) contain the same active ingredient (bupropion) found in ZYBAN, which is used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended-release tablets (XL) should not be used in combination with ZYBAN or any other medications that contain bupropion hydrochloride (such as WELLBUTRIN SR, the extended-release form 250 mg twice daily increased exposures (C_{max} and AUC) of bupropion by 40% and 60% for clopidogrel, by 38% and 85% for ticlopidine, respectively. The exposures of hydroxybupropion were decreased. WELLBUTRIN, the immediate-release formulation, and APLENZIN, a bupropion hydrobromide formulation). In addition, there are a number of generic bupropion HCI products for the immediate, sustained, and extended-

Potential for Cognitive and Motor Impairment

Advise patients that any CNS-active drug like bupropion hydrochloride extended-release tablets (XL) may Cimetidine: Following oral administration of bupropion 300 mg with and without cimetidine 800 mg in 24 impair their ability to perform tasks requiring judgment or motor and cognitive skills. Advise patients that until they are reasonably certain that bupropion hydrochloride extended-release tablets (XL) do not adversely affect However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of heir performance, they should refrain from driving an automobile or operating complex, hazardous machinery Bupropion hydrochloride extended-release tablets (XL) treatment may lead to decreased alcohol tolerance.

Concomitant Medications sel patients to notify their healthcare provider if they are taking or plan to take any prescription or overthe-counter drugs, because bupropion hydrochloride extended-release tablets (XL) and other drugs may affect

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during

 C_{max} by 57%. The AUC and C_{max} of hydroxybupropion metabolite were decreased by 50% and 31%, respectively. through human milk. Instruct patients to immediately contact the infant's healthcare provider if they note any side effect in the infant that concerns them or is persistent

> ruct patients to swallow bupropion hydrochloride extended-release tablets (XL) whole so that the release rate is not altered. Instruct patients if they miss a dose, not to take an extra tablet to make up for the missed dose and to take the next tablet at the regular time because of the dose-related risk of seizure. Instruct patients that bupropion hydrochloride extended-release (XL) tablets should be swallowed whole and not crushed, divided, or chewed. Bupropion hydrochloride extended-release tablets (XL) should be administered in the

Manufactured for:

Manufactured by:

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bupropion hydrochloride extended-release tablets (XL) and contact a healthcare professional if they experience such symptoms [see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]

Patients should be advised that taking bupropion hydrochloride extended-release tablets (XL) can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Preisting glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and

Ritonavir and Loninavir: In a healthy volunteer study, ritonavir 100 mg twice daily reduced the AUC and C_{ma} of bupropion by 22% and 21%, respectively. The exposure of the hydroxybupropion metabolite was decreased

<u>Precautions for Nursing Mothers</u>
Communicate with the patient and pediatric healthcare provider regarding the infant's exposure to bupropion

morning and may be taken with or without food.

TWi Pharmaceuticals USA, Inc.

In vitro, buppropion and hydroxybupropion are CYP2D6 inhibitors. In a clinical study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of CYP2D6, bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max} AUC, and $T_{1/2}$ of desipramine by an average of approximately 2- 5- and 2-fold, respectively. The effect was present for at least 7 days after the last dos of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally

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Severe Allergic Reactions