

NDA 21-515
WELLBUTRIN XL[®] (bupropion hydrochloride) Extended-Release Tablets
Antidepressant of the Aminoketone Class
Biovail Technologies, Ltd.
700 Route 202/206 North
Bridgewater, NJ 08807

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

The goal of this REMS is to inform patients about the serious risks of associated with the use of WELLBUTRIN XL[®].

II. REMS ELEMENTS:

A. Medication Guide

Biovail in accordance with 21 CFR 208.24 will make the Medication Guide available for distribution to patients. The currently approved Medication Guide will be dispensed with each WELLBUTRIN XL prescription. The Medication Guide is provided on each unit-of-use bottle; the bottle label contains an attached extended content label containing the Medication Guide text. Because the Medication Guide is included as part of the primary package for WELLBUTRIN XL, Biovail has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide.

In accordance with 21 CFR 208.24(d), a statement will be included on the container label for WELLBUTRIN XL for the unit of use bottles.

B. Timetable for Submission of Assessments

GlaxoSmithKline will submit REMS Assessments to FDA 18 months, 3 years and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

GlaxoSmithKline will submit each assessment so that it will be received by the FDA on or before the due date.

MEDICATION GUIDE

WELLBUTRIN XL® (WELL byu-trin)

(bupropion hydrochloride extended-release tablets)

Read this Medication Guide carefully before you start using WELLBUTRIN XL and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about WELLBUTRIN XL, ask your doctor or pharmacist.

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 quit smoking; and the third section is entitled "What Other Important Information Should I Know About WELLBUTRIN XL?"

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

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

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

- 1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
- 2. Depression and 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 actions.
- 3. 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 the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.

- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a 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
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant 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.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

WELLBUTRIN XL has not been studied in children under the age of 18 and is not approved for use in children and teenagers.

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

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 WELLBUTRIN XL is not a treatment for quitting smoking, it contains the same active ingredient (bupropion hydrochloride) as ZYBAN[®] which is used to help patients quit smoking.

Some people have had changes in behavior, hostility, agitation, depression, suicidal thoughts or actions while taking bupropion to help them quit smoking. These symptoms can develop during treatment with bupropion or after stopping treatment with bupropion.

If you, your family member, or your caregiver notice agitation, hostility, depression or changes in thinking or behavior that are not typical for you, or you have any of the following symptoms, stop taking bupropion and call your healthcare provider right away:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior or mood

When you try to quit smoking, with or without bupropion, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or 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.

Before taking bupropion, tell your healthcare provider if you have ever had depression or other mental illnesses. You should also tell your doctor 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 WELLBUTRIN XL?

- **Seizures: There is a chance of having a seizure (convulsion, fit) with WELLBUTRIN XL, especially in people:**
 - with certain medical problems.
 - who take certain medicines.

The chance of having seizures increases with higher doses of WELLBUTRIN XL. For more information, see the sections “Who should not take WELLBUTRIN XL?” and “What should I tell my doctor before using WELLBUTRIN XL?” Tell your doctor about all of your medical conditions and all the medicines you take. **Do not take any other medicines while you are using WELLBUTRIN XL unless your doctor has said it is okay to take them.**

If you have a seizure while taking WELLBUTRIN XL, stop taking the tablets and call your doctor right away. Do not take WELLBUTRIN XL again if you have a seizure.

- **High blood pressure (hypertension).** Some people get high blood pressure, that can be severe, while taking WELLBUTRIN 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.
- **Severe allergic reactions.** Some people have severe allergic reactions to WELLBUTRIN XL. Stop taking WELLBUTRIN XL and call your doctor 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 reaction.
- **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while taking WELLBUTRIN 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 your doctor.

What is WELLBUTRIN XL?

WELLBUTRIN XL is a prescription medicine used to treat adults with a certain type of depression called major depressive disorder and for prevention of autumn-winter seasonal depression (seasonal affective disorder).

Who should not take WELLBUTRIN XL?

Do not take WELLBUTRIN XL if you:

- have or had a seizure disorder or epilepsy.
- **are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as WELLBUTRIN® Tablets or WELLBUTRIN SR® Sustained-Release Tablets.** Bupropion is the same active ingredient that is in WELLBUTRIN XL.
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- have taken within the last 14 days medicine for depression called a monoamine oxidase inhibitor (MAOI), such as NARDIL®*(phenelzine sulfate), PARNATE®(tranylcypromine sulfate), or MARPLAN®*(isocarboxazid).
- have or had an eating disorder such as anorexia nervosa or bulimia.
- are allergic to the active ingredient in WELLBUTRIN XL, bupropion, or to any of the inactive ingredients. See the end of this leaflet for a complete list of ingredients in WELLBUTRIN XL.

What should I tell my doctor before using WELLBUTRIN XL?

- Tell your doctor if you have ever had depression, suicidal thoughts or actions, or other mental health problems. See "Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions."
- **Tell your doctor about your other medical conditions including if you:**
 - **are pregnant or plan to become pregnant.** It is not known if WELLBUTRIN XL can harm your unborn baby.
 - **are breastfeeding.** WELLBUTRIN XL passes through your milk. It is not known if WELLBUTRIN XL can harm your baby.
 - **have liver problems,** especially cirrhosis of the liver.
 - have kidney problems.
 - have an eating disorder such as anorexia nervosa or bulimia.
 - have had a head injury.
 - 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 pressure.
 - are a diabetic taking insulin or other medicines to control your blood sugar.
 - drink a lot of alcohol.
 - abuse prescription medicines or street drugs.
- **Tell your doctor about all the medicines you take,** including prescription and non-prescription 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 using WELLBUTRIN XL.

How should I take WELLBUTRIN XL?

- Take WELLBUTRIN XL exactly as prescribed by your doctor.
- **Do not chew, cut, or crush WELLBUTRIN XL tablets.** You must swallow the tablets whole. **Tell your doctor if you cannot swallow medicine tablets.**
- Take WELLBUTRIN XL at the same time each day.
- Take your doses of WELLBUTRIN XL at least 24 hours apart.
- You may take WELLBUTRIN XL with or without food.
- If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and take your next tablet at the regular time. **This is very important.** Too much WELLBUTRIN XL can increase your chance of having a seizure.

- If you take too much WELLBUTRIN XL, or overdose, call your local emergency room or poison control center right away.
- The WELLBUTRIN XL tablet is covered by a shell that slowly releases the medicine inside your body. You may notice something in your stool that looks like a tablet. This is normal. This is the empty shell passing from your body.
- **Do not take any other medicines while using WELLBUTRIN XL unless your doctor has told you it is okay.**
- If you are taking WELLBUTRIN XL for the treatment of major depressive disorder, it may take several weeks for you to feel that WELLBUTRIN XL is working. Once you feel better, it is important to keep taking WELLBUTRIN XL exactly as directed by your doctor. Call your doctor if you do not feel WELLBUTRIN XL is working for you.
- If you are taking WELLBUTRIN XL for the prevention of seasonal major depressive episodes associated with seasonal affective disorder, it is important to keep taking WELLBUTRIN XL through the autumn-winter season, or as directed by your doctor.
- Do not change your dose or stop taking WELLBUTRIN XL without talking with your doctor first.

What should I avoid while taking WELLBUTRIN XL?

- Do not drink a lot of alcohol while taking WELLBUTRIN XL. If you usually drink a lot of alcohol, talk with your doctor 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 WELLBUTRIN XL affects you. WELLBUTRIN XL can impair your ability to perform these tasks.

What are possible side effects of WELLBUTRIN XL?

WELLBUTRIN XL can cause serious side effects. Read this entire Medication Guide for more information about these serious side effects.

Common side effects reported in studies of major depressive disorder include weight loss, loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more often. In studies of seasonal affective disorder, common side effects included weight loss, constipation, and gas.

If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your medicine too close to bedtime.

These are not all the side effects of WELLBUTRIN XL. For a complete list, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or BTA Pharmaceuticals at 866-246-8245 (opt. 3).

How should I store WELLBUTRIN XL?

- Store WELLBUTRIN XL at room temperature. Store out of direct sunlight. Keep WELLBUTRIN XL in its tightly closed bottle.
- WELLBUTRIN XL tablets may have an odor.

General Information about WELLBUTRIN XL.

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use WELLBUTRIN XL for a condition for which it was not prescribed. Do not give WELLBUTRIN XL to other people, even if they have the same symptoms you have. It may harm them. Keep WELLBUTRIN XL out of the reach of children.

This Medication Guide summarizes important information about WELLBUTRIN XL. For more information, talk with your doctor. You can ask your doctor or pharmacist for information about WELLBUTRIN XL that is written for health professionals or call toll-free 866-246-8245 (opt. 3).

What are the ingredients in WELLBUTRIN XL?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: ethylcellulose aqueous dispersion, glyceryl behenate, methacrylic acid copolymer dispersion, polyvinyl alcohol, polyethylene glycol, povidone, silicon dioxide, and triethyl citrate. The tablets are printed with edible black ink.

*The following are registered trademarks of their respective manufacturers: ZYBAN[®]/GlaxoSmithKline; NARDIL[®]/Warner Lambert Company; PARNATE[®]/GlaxoSmithKline; MARPLAN[®]/Validus Pharmaceuticals, LLC; WELLBUTRIN[®] and WELLBUTRIN XL[®]/GlaxoSmithKline

Rx Only

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

Manufactured by:
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For:
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Bridgewater, NJ 08807

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Application
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Product Name

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SUPPL-25

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WELLBUTRIN XL(BUPROPION
HCL)EXTENDED REL

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/s/

THOMAS P LAUGHREN
02/26/2010