

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200063Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
RISK EVALUATION AND MITIGATION STRATEGY REVIEW**

Date: May 5, 2014

Reviewer(s) Joyce Weaver, Pharm.D., Risk Management Analyst
Division of Risk Management (DRISK)

Team Leader Cynthia LaCivita, Pharm.D., Team Leader, DRISK

Division Director: Claudia Manzo, Pharm.D., Director, DRISK

Subject: Review to determine if a REMS is necessary

Drug Name(s): Contrave (Naltrexone HCl and bupropion HCl) Extended-Release Tablets

Therapeutic class & dosage form: Treatment of obesity
Tablets, 8mg naltrexone/90mg bupropion

OND Review Division Division of Metabolism and Endocrinology Products

Application Type/Number: NDA 200063

Application received December 10, 2013

PDUFA/Action Date June 11, 2014

Applicant/sponsor: Orexigen

OSE RCM #: 2014-230

TSI #: n/a

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review by the Division of Risk Management evaluates if a Risk Evaluation and Mitigation Strategy (REMS) is needed for the Contrave (naltrexone and bupropion) extended-release tablets. The proposed indication for Contrave is for weight loss and maintenance of weight loss in patients with an initial body mass index (BMI) of 30 kg/m² or 27 mg/m² in the presence of at least one weight-related co-morbidity (e.g., diabetes, hypertension, hyperlipidemia).

In this review cycle, Orexigen did not propose a REMS for Contrave. The sponsor proposed a REMS comprising a communication plan and a Medication Guide during the previous review cycle. The previous REMS proposal was submitted at the end of the previous review cycle, and the REMS was not reviewed before the Complete Response (CR) letter was issued, 10 days after the submission of the REMS.

1.1 BACKGROUND

Orexigen re-submitted the application for Contrave, a combination product containing two already-approved drugs, naltrexone and bupropion. Naltrexone is approved for the treatment of opioid addiction (approval in 1984) and alcohol dependence (approval in 1995). The usual naltrexone dose is 50 mg orally daily. Naltrexone is also available as an injectable suspension for the treatment of alcohol dependence. Bupropion (Wellbutrin, Wellbutrin SR, and Wellbutrin XL) is currently approved for the treatment of depression and seasonal affective disorder, and (Zyban) as an aid to smoking cessation treatment (approval in 1997). The usual Wellbutrin SR dose is 300 mg daily. Generic versions of both naltrexone and bupropion have been approved.

The proposed dosage of Contrave is one tablet daily (8mg naltrexone/90mg bupropion) initially, titrated over 4 weeks to 2 tablets twice daily.

1.2 REGULATORY HISTORY

Orexigen first submitted an application for Contrave on March 31, 2010. The application included a REMS comprising a Medication Guide, and a timetable for submission of assessments. The application was considered at a December 7, 2010 meeting of Endocrine and Metabolic Drugs Advisory Committee (EMDAC). The committee voted 13 yes and 7 no supporting approval of the application.

On January 19, 2011, shortly before the PDUFA action date, the sponsor submitted a REMS comprising a Medication Guide, a communication plan, and a timetable for submission of assessments. This submission was not reviewed prior to issuance of the CR letter. The Agency issued a CR letter January 31, 2011, citing the pre-approval need for a randomized, double-blind, placebo-controlled cardiovascular outcomes trial (CVOT). The CR letter acknowledged the sponsor's REMS submission, and agreed that a REMS would likely be needed, should Contrave be approved, to address seizure-related adverse events and suicidal thoughts and behaviors.

The sponsor pursued dispute resolution regarding the need to conduct a pre-approval CVOT. They proposed (b) (4)

(b) (4)
The Agency denied the appeal. (b) (4)
to address the cardiovascular uncertainty was not an appropriate path forward in the absence of additional safety data. The Agency agreed to review a resubmitted application that included interim results from the CVOT.

In a subsequent meeting on March 11, 2013, the sponsor asked the Agency whether a REMS would likely be required for Contrave, or whether this decision would be dependent on the interim results from the CVOT. The Agency responded that a REMS was not likely to be needed, but would depend on the review of all data submitted with the application.

The sponsor resubmitted the application with interim results from the CVOT on December 10, 2013. The Prescription Drug User Fee Act (PDUFA) goal action date for the application is June 11, 2014.

REMS for other bupropion products

The anti-depressant drugs, including Wellbutrin, Wellbutrin SR, and Wellbutrin XL, had REMS comprising Medication Guides and timetables for submission of assessments to address the risk of suicidality. The REMS for the Wellbutrin products were released August 2, 2012. The decision to release the REMS for the Wellbutrin products was based on a determination that maintaining the Medication Guides as part of labeling was adequate to address the risk.

A REMS for Zyban comprising a Medication Guide and a timetable for submission of assessments was approved in February 2010. The REMS was modified in March 2013 to change the wording of the goal so that it was clear that the REMS was directed at the potential serious risk of neuropsychiatric adverse events associated with the use of Zyban. The Zyban REMS was eligible to be released based on the results of the 3-year REMS Assessment report, and consideration was given to releasing this REMS. However, the REMS was not released pending the results of a phase-4, randomized, double-blind, active- and placebo-controlled, multicenter trial evaluating the neuropsychiatric safety and efficacy of 12 weeks of varenicline tartrate 1mg bid and bupropion hydrochloride 150 mg bid for smoking cessation in subjects with and without a history of psychiatric disorders. Like Zyban, Chantix (varenicline) has a REMS comprising a Medication Guide and a timetable for submission of assessments.

2 MATERIALS REVIEWED

We reviewed the following:

- REMS submitted with March 31, 2010 application comprising a Medication Guide and a timetable for submission of assessments
- Previously proposed REMS dated January 19, 2011 comprising a communication plan, a Medication Guide, and a timetable for submission of assessments
- Complete response letter January 31, 2011
- June 27, 2011 meeting minutes for meeting between sponsor and Agency May 26, 2011

- July 7, 2011 ODE II letter denying appeal to dispute resolution for requirement for pre-approval CVOT, signed by C. Rosebraugh
- October 15, 2012 CDER letter denying appeal to dispute resolution for requirement for pre-approval CVOT, signed by D. Throckmorton
- April 9, 2013 meeting minutes for meeting between sponsor and Agency March 11, 2013
- January 31, 2011 Clinical Review of Contrave application, E. Craig
- Clinical briefing document for December 7, 2010 meeting of Endocrine and Metabolic Drugs Advisory Committee
- Proposed draft labeling submitted with December 2013 resubmission

Additionally, the following documents informed our review:

- Review of 3-year REMS Assessment Report for Zyban, April 26, 2013; B. Gordon and D. Auth
- Letter releasing REMS for Wellbutrin products, August 2, 2012
- Wellbutrin SR prescribing information
- Draft Guidance for Industry, *Developing Products for Weight Management*

3 RESULTS OF REVIEW

3.1 OVERVIEW OF DEVELOPMENT PROGRAM

The efficacy and safety of Contrave were assessed in four placebo-controlled one-year trials in overweight and obese patients, and in obese subjects with type 2 diabetes. Approximately 3,200 patients were randomized to receive Contrave and 1,500 patients were randomized to placebo. Patients had body mass index (BMI) ≥ 30 kg/m² or ≥ 27 kg/m² with at least 1 weight-related co-morbidity (hypertension, dyslipidemia, diabetes). The primary endpoints were mean change from baseline body weight and the proportion of individuals who achieved a $\geq 5\%$ reduction in body weight.

About 35% of patients in the Contrave-treated groups achieved a $\geq 5\%$ reduction in body weight, about twice that in the placebo group. This meets the categorical standard for efficacy set out by the FDA in the 2007 draft guidance for industry, *Developing Products for Weight Management*. The difference in mean weight loss between the Contrave-treated patients and patients receiving placebo was 3.7%, less than the 5% standard for efficacy set out by the FDA. According to the draft guidance, a product should meet at least one of the criteria to be approved; it is not necessary to meet both criteria.

3.2 SAFETY CONCERNS

Naltrexone can cause liver injury when used in large doses. The amount of naltrexone in Contrave (8mg per tablet; dose titrated to 16mg bid) is not believed to be likely to induce liver injury¹.

¹ January 31, 2011 Clinical Review of Contrave application, E. Craig.

The most concerning safety issues for bupropion are seizures, psychiatric events, neurologic/cognitive events, and hypertension.

Seizures

The risk of seizure is believed to be dose-related, and might be related to large increases in dose. The Wellbutrin SR² prescribing information cites an incidence of seizure of 0.1% (1/1,000) when Wellbutrin SR is dosed up to 300 mg per day, and the incidence increases to 0.4% (4/1,000) at the maximum recommended dose of 400 mg per day. The Wellbutrin SR prescribing information states that the risk of seizure can be reduced if the dose of Wellbutrin SR does not exceed 400 mg per day, is administered in divided doses of 200 mg twice daily, and the titration rate to increase the dose is gradual.

Patients with a seizure history or at increased risk for seizures were excluded from the Contrave trials. In the trials, two patients (2/3239, 0.06%) receiving Contrave had a seizure. Neither patient had a seizure history prior to entering into the trial. One seizure was believed to be related to hypoglycemia.

Psychiatric events

The bupropion products contain a boxed warning for suicidal thoughts and behaviors, and neuropsychiatric reactions. Serious neuropsychiatric symptoms have been reported not only in patients taking bupropion for depression, but also for patients taking bupropion for smoking cessation. These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide.

In the Contrave clinical trials, there were no completed suicides or suicide attempts. There were four events of suicidal ideation or behavior during this trial, one event (1/3239, <0.1%) in the Contrave treatment group compared to three events (3/1515, 0.2%) in the placebo group.

Dr. Craig, the reviewing Medical Officer for Contrave, made the following points about psychiatric events in the Contrave clinical trial data³:

- There were a higher percentage of subjects with psychiatric events in the Contrave patients compared with the patients receiving placebo (20.8% and 15.5%, respectively).
- Psychiatric events were seen more often in subjects with a prior history of depression or anxiety in both Contrave and placebo groups than in subjects without a prior history.

² Wellbutrin SR labeling referenced instead of Wellbutrin or Wellbutrin XL because the dosing interval for Wellbutrin SR is the same as proposed for Contrave.

³ Summary list adapted from 2010 EMDAC briefing book.

- Incidence of depression was similar between treatment groups (6.0% Contrave and 5.9% placebo).
- Anxiety was greater in the Contrave group compared to placebo (5.7% Contrave and 4.4% placebo).
- Psychosis was higher in the Contrave group compared with placebo (0.8% Contrave and <0.1% placebo). The placebo group had only one report of potential psychosis (depersonalization) and no reports of psychosis events.

Neurologic/cognitive events

The Wellbutrin SR prescribing information does not specifically describe cognitive events, except to counsel patients that cognitive effects could occur with use, as can occur with “any CNS-active drug.” Dr. Craig summarized the following from the clinical trial data for Contrave⁴.

- There was a greater incidence of cognitive events in the Contrave group compared to the placebo group (5.1% vs. 2.0%).
- 1.1% of the Contrave group versus 0.4% of placebo subjects discontinued for a cognitive event
- The most common cognitive event was attention disorders (2.3% Contrave vs. 0.6% placebo)
- Dizziness was common in Contrave treated patients (10%) and almost 3 times more frequent than in placebo (3.4%).
- Three patients in the Contrave group discontinued due to syncope compared to zero in placebo.

Hypertension

The Wellbutrin SR prescribing information states bupropion can increase blood pressure, especially in patients with pre-existing hypertension. The draft Contrave labeling contains the following language, proposed by the Agency.

In an ambulatory blood pressure monitoring substudy of 182 patients, the mean change from baseline in systolic blood pressure after 52 weeks of treatment was -0.2 mm Hg for the Contrave group and -2.8 mm Hg for the placebo group (treatment difference was 2.6 mm Hg, p=0.08). For this same group, the mean change in diastolic blood pressure was 0.8 mm Hg for the Contrave group and -2.1 mm Hg for the placebo group (treatment difference was 2.9 mm Hg, p=0.004).

A greater percentage of subjects experienced increased blood pressure and heart rate adverse reactions in the Contrave group compared to the placebo group (6.3% vs 4.2%, respectively). This was primarily attributable to Hypertension/Blood

⁴ Summary list adapted from 2010 EMDAC briefing book.

Pressure Increased adverse reactions (5.9% Contrave and 4.0% placebo). These events were observed in both patients with and without evidence of preexisting hypertension.

The clinical significance of blood pressure and heart rate elevation with Contrave treatment is unclear, especially for patients with cardiac and cerebrovascular disease (such as patients with a history of myocardial infarction or stroke in the previous 6 months, life-threatening arrhythmias, or congestive heart failure). Blood pressure and pulse should be measured prior to starting therapy with Contrave and should be monitored at regular intervals consistent with usual clinical practice. Contrave should be given with caution to those patients with controlled hypertension and should not be given to patients with uncontrolled hypertension.

3.3 RISK MANAGEMENT PROPOSED BY THE SPONSOR

The sponsor did not submit a REMS for Contrave with the resubmission.

4 DISCUSSION OF A REMS

The safety issues with Contrave include the safety issues for the ingredients, naltrexone and bupropion. The safety issues associated with bupropion are the salient issues for Contrave, including seizures, psychiatric events, neurologic/cognitive events, and hypertension. The bupropion products have a boxed warning for suicidality and for neuropsychiatric events. Contrave will likewise have a boxed warning.

All the bupropion products previously had REMS with a Medication Guide as the sole mitigation tool (the REMS also had a timetable for submission of assessments). The REMS for the bupropion products have been released, except for Zyban. Although the Zyban REMS was eligible for release based on the 3-year REMS assessment, a decision was made to keep the Zyban REMS in place pending completion of a phase-4 trial comparing the neuropsychiatric events of Zyban and Chantix. If it was determined a REMS was necessary for Contrave, the REMS required would likely be that previously required for all the approved bupropion products.

REMS for 144 products have been released from the requirement for a REMS. Most of these products previously had REMS with a Medication Guide as the sole risk mitigation tool and most of these have been released. The last Medication Guide-only REMS was approved April 29, 2011 (Androgel). The products that were released from Medication Guide-only REMS still have required Medication Guides included as part of the labeling.

With release of the REMS, the requirement for the sponsor to assess patient understanding of the risk is removed, but dispensing of the Medication Guide is still required. The requirement to distribute the Medication Guide as part of labeling or as an element of the REMS follows 21 CFR 208.24 . Only the testosterone products and the smoking cessation products, Zyban and Chantix, still have REMS with a Medication Guide as the sole risk mitigation tool.

Contrave will have a Medication Guide for patients. DRISK believes the Medication Guide, dispensed outside a REMS, is sufficient to convey risk to patients. DRISK does not believe it is necessary to require a REMS for Contrave.

5 CONCLUSION/RECOMMENDATION

We do not recommend that a REMS be required for Contrave at this time. We believe that labeling, including a Medication Guide, is sufficient to mitigate the risks associated with Contrave.

We ask that DMEP include DRISK in future discussions regarding this issue.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE P WEAVER
05/05/2014

CLAUDIA B MANZO
05/05/2014
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS

NDA/BLA #s: 200063
Products: CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) Extended-Release tablets 4mg/90mg, 8mg/90mg
APPLICANT: Orexigen Therapeutics
FROM: Eric Colman, M.D.
DATE: January 4, 2011

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) to ensure that the benefits of the drug outweigh the risks of seizure-related adverse events, and suicidal thoughts or behaviors. In reaching this determination, we considered the following:

- A. Approximately two out of three adults in the United States are considered overweight (BMI 25 to 29.9 kg/m²) or obese (≥ 30 kg/m²). This estimate is based on the 2007-2008 National Health and Nutrition Examination Survey database published in the Journal of American Medical Association in January 2010. Phentermine, a drug approved for short-term weight loss, (b) (4) weight loss drug with approximately (b) (4) prescriptions dispensed in outpatient retail pharmacy settings in 2009.
- B. Obesity is associated with numerous co-morbidities, including dyslipidemia, coronary artery disease, hypertension, stroke, and type 2 diabetes mellitus. The second leading modifiable risk factor for death in the United States is being overweight.

- C. The benefit of CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) is expected increased weight loss over lifestyle modification and modest improvements in some weight-related co-morbidities. The effect of pharmacological weight-loss on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.
- D. The expected duration of therapy is over a patient's lifetime.
- E. In addition to the most serious risks of seizure-related adverse events, and suicidal thoughts or behaviors, bupropion, a component of CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride), has been associated with other psychiatric adverse events (insomnia, anxiety, agitation), anaphylactic reactions/rash, and hypertension. In clinical trials of CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) increases in serum creatinine and neurocognitive adverse events (attention and thinking disorders, and dizziness) were also noted.
- F. CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride). FDA has determined that CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride). FDA has determined that CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) is a product for which patient labeling could help prevent serious adverse effects. FDA has determined that CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride).

The elements of the REMS will be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
01/25/2011

ERIC C COLMAN
01/26/2011

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

DEFER COMMENT MEMO

Date: December 21, 2010

To: Mary Parks, MD, Director
Division of Metabolic and Endocrinology Products
(DMEP)

Through: Suzanne Robottom, PharmD, Team Leader
Risk Management Analyst (RMA)
Office of Surveillance and Epidemiology (OSE)
Division of Risk Management (DRISK)

From: **Scientific Lead**
Joyce Weaver, PharmD.
Risk Management Analyst (RMA), DRISK

DRISK Review Team
Mary Dempsey, BS
Risk Management Programs Coordinator, DRISK

Shawna Hutchins, MPH, BSN, RN
Patient Labeling Reviewer, DRISK

Subject: Defer Comment on the proposed Risk Evaluation and
Mitigation Strategy (REMS) and Patient Labeling,
Medication Guide (MG)

**Drug Name (Established
Name):** Contrave (naltrexone HCL and bupropion HCL)

Dosage and Route: Tablet, Extended Release

Application Type/Number: NDA 200063

Applicant/Sponsor: Orexigen Therapeutics, Inc.

OSE RCM #: 2010-802

This document is to defer comment on the proposed Risk Evaluation and Mitigation strategy (REMS) and Medication Guide for Contrave (naltrexone HCL and bupropion HCL).

On April 13, 2010 the Division of Division of Metabolic and Endocrinology Products (DMEP) requested that the Division of Risk Management (DRISK) review the proposed Risk Evaluation and Mitigation Strategy (REMS) and Medication Guide (MG) for Contrave (naltrexone HCL and bupropion HCL) submitted March 31, 2010 with the original New Drug Application 200063 for the proposed treatment of obesity.

Due to outstanding clinical deficiencies, DMEP plans to issue a Complete Response (CR) letter. DMEP does not plan to address labeling or REMS during this review cycle. Therefore, DRISK defers our review of the Medication Guide and the REMS. A final discussion on the appropriate risk management strategy will be undertaken after the sponsor submits a satisfactory response to the Complete Response (CR) letter.

Please send DRISK a new consult request at such time. This memo serves to close the existing consult request under NDA 20063 Contrave (naltrexone HCL and bupropion HCL) extended release tablets.

Please notify DRISK if you have any questions.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY J DEMPSEY
12/21/2010

SUZANNE C BERKMAN ROBOTOM
12/21/2010
I concur.