

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200063Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 200063
Product Name: CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets

PMR/PMC Description: A juvenile animal study with the combination of bupropion and naltrexone to assess post-natal growth and development with additional assessment of behavior, learning and memory.

PMR/PMC Schedule

Milestones:	Final Protocol Submission:	<u>July 2015</u>
	Study/Trial Completion:	<u>December 2016</u>
	Final Report Submission:	<u>March 2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A juvenile animal study with the combination of bupropion and naltrexone, both centrally-active drugs, is considered necessary to assess for potential adverse outcomes or irreversible adverse effects on learning/memory/behavioral development and sexual maturation as a result of exposure during the pre-pubertal and pubertal period. Results of this study are required prior to initiating pediatric efficacy and safety studies. These data are not necessary to support approval of this drug for use in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Naltrexone, an opioid receptor antagonist, and bupropion, a modulator of dopamine, norepinephrine, and serotonin, are CNS active drugs with the potential to cause adverse outcomes or irreversible effects on learning/memory/behavioral development as a result of exposure during the pre-pubertal/pubertal period. Neither drug has been studied in juvenile animals. Hydroxybupropion, the major active metabolite of bupropion in humans, has pharmacological activity and therefore also has the potential to cause behavior, learning, and memory changes in pre-pubertal/pubertal animals and humans. The effects naltrexone, bupropion, and hydroxybupropion on learning/memory/behavioral development should be assessed in juvenile animals prior to initiating pediatric efficacy and safety studies. Metabolism of bupropion in mice appears to be more similar to humans regarding exposure to hydroxybupropion than rats, and appears to be the more suitable species for evaluation. Endpoints to be addressed include standard clinical pathology and toxicity endpoints, motor activity, learning and memory, growth, sexual maturation, and mating and fertility. The study design should incorporate assessment of reversibility after a drug-free period and toxicokinetic exposure.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A juvenile animal study with the combination of bupropion and naltrexone to assess behavior, learning and memory, growth, sexual maturation, and mating/fertility. The study should include the evaluation of the CNS-active major human metabolite hydroxybupropion.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks

- Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

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- Assess signals of serious risk related to the use of the drug?
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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical pharmacology study (or substudy) under Pediatric Research Equity Act (PREA) to assess pharmacokinetics (PK) and pharmacodynamic (PD) parameters related to naltrexone/bupropion in pediatric patients ages 12 to 17 (inclusive). Data from this study should be considered when choosing final dose(s) for assessing safety and efficacy in this pediatric population. The subjects from this substudy should be allowed to enroll in the safety and efficacy trial. The safety and efficacy trial is a 52-week randomized, double-blind, placebo-controlled pediatric trial under PREA to evaluate the safety and efficacy of naltrexone/bupropion for the treatment of obesity in pediatric patients ages 12 to 17 (inclusive). The study population should consist of pediatric patients with obesity, ages ≥ 12 to ≤ 17 years, with one or more weight-related co-morbidities (controlled hypertension, diabetes, or dyslipidemia) with BMI above the 95th percentile based on age and sex and not greater than 44 kg/m². Subjects with genetic or endocrine causes of obesity should be excluded. Adequate representation from both male and female adolescents should be included and subjects must have a documented history of failure to lose sufficient weight with lifestyle modification alone. Safety assessments should include monitoring for heart rate changes and neurocognitive adverse effects. Part B of this study will not be initiated until results from the juvenile animal study have been submitted and reviewed by the Agency.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
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- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

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If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical pharmacology study (or substudy) under Pediatric Research Equity Act (PREA) to assess pharmacokinetics (PK) and pharmacodynamic (PD) parameters related to naltrexone/bupropion in pediatric patients ages 7 to 11 (inclusive). Data from this study should be considered when choosing final dose(s) for assessing safety and efficacy in this pediatric population. The subjects from this substudy should be allowed to enroll in the safety and efficacy trial. The safety and efficacy trial is a 52-week randomized, double-blind, placebo-controlled pediatric trial under PREA to evaluate the safety and efficacy of naltrexone/bupropion for the treatment of obesity in pediatric patients ages 7 to 11 (inclusive). The safety and efficacy study should enroll children, ages 7 - 11 years (inclusive), with age- and sex-matched BMI \geq 99th percentile with a major co-morbidity. Subjects must have a documented history of failure to lose sufficient weight with comprehensive multidisciplinary intervention. Subjects with obesity associated with known endocrine or genetic causes should be excluded. Safety assessments should include monitoring for heart rate changes and neurocognitive adverse effects. Part B of this study will not be initiated until results from the adolescent pharmacokinetics, safety, and efficacy trial have been submitted and reviewed by the Agency.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
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Agreed upon:

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 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
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 - Nonclinical study, not safety-related (specify)
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- There is not enough existing information to assess these risks
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- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A thorough QT study designed to rule out small changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms), as defined by ICH E14 guidance.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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(signature line for BLAs)

The LIGHT trial was initiated to address Contrave’s approval deficiency described in the CR letter: “In general, in your phase 3 clinical trials, mean systolic and diastolic blood pressure and heart rate were statistically significantly higher in naltrexone/bupropion-treated subjects compared with placebo-treated subjects. In addition, there were more adverse events related to hypertension in the naltrexone/bupropion groups, particularly in subjects with type 2 diabetes. These findings raise concern about the cardiovascular safety profile of naltrexone/bupropion when used long-term in a population of overweight and obese subjects. Therefore, before your application can be approved, you must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug’s benefit-risk profile.” As noted above, the interim safety results of the LIGHT trial provide sufficient evidence that Contrave does not unacceptably increase cardiovascular risk to support approval.

During review of the current submission, the Agency became aware of an unacceptable degree of unblinding both within and outside of Orexigen, which far exceeded the intent of the original Data Access Plan. This raised significant concerns about the possibility of more widespread dissemination of the interim data and its potential impact on the reliability of any data collected from the time of dissemination onward. The Agency was not confident that it would ultimately be able to detect or exclude the possibility that these activities may have biased the trial’s results or otherwise comprised its integrity and thus concluded that the LIGHT trial, by itself, could not satisfy a post-marketing requirement (PMR) related to cardiovascular safety. A new cardiovascular outcome trial (CVOT) is required.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
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– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with Contrave on the incidence of major adverse cardiovascular events (MACE) in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors. The primary objective of this trial should be to demonstrate that the upper bound of the 2-sided confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with CONTRAVE to that observed in the placebo group is less than 1.4. The trial should be designed to provide sufficient data to reflect the "on-treatment" cardiovascular risk associated with Contrave. Sample size calculation should take into account that "on-study" events would be censored 365 days after treatment discontinuation. The ongoing LIGHT trial will not be sufficient to meet this requirement; a new trial is required.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
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 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
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5. Is the PMR/PMC clear, feasible, and appropriate?

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If so, does the clinical trial meet the following criteria?

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PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 200063
Product Name: CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets

PMR/PMC Description: Conduct a single-dose pharmacokinetic trial in subjects with mild, moderate, and severe hepatic impairment. Include overweight and obese subjects in the trial population.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	September 2015
	Study/Trial Completion:	<u>November 2017</u>
	Final Report Submission:	<u>August 2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Only patients with hepatic impairment will be affected by lack of this knowledge. Availability of this information will help in guiding better dosing decision for Contrave in this specific population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The purpose of this PMR is to identify an unexpected risk of increased or more severe serious adverse events in patients with hepatic impairment treated with Contrave, due to altered kinetics of the drug in these patients.

The effect of hepatic impairment on pharmacokinetics of bupropion and naltrexone from Contrave is not fully understood. Bupropion undergoes extensive metabolism in liver to hydroxybupropion (AUC based Metabolite-to-parent ratio of 12 at steady-state), threohydrobupropion (AUC based Metabolite-to-parent ratio of 4 at steady-state), and erythrohydrobupropion (AUC based Metabolite-to-parent ratio of 1 at steady-state). Orally administered naltrexone is metabolized extensively by non-CYP pathways (aldo-keto-reductases) to 6-beta naltrexol (AUC based Metabolite-to-parent ratio of 30 at steady-state). Bupropion and metabolites as well as naltrexone and its metabolite are renally excreted. The current bupropion and naltrexone product labels indicate a potential for significant increase in exposure of bupropion/naltrexone and its metabolites, although to a different magnitude for each of these components. However, the information is limited from a quantitative perspective in precisely guiding the dosing across varying degree of hepatic impairment. Further, the risk of seizures with bupropion is higher for 400 mg daily dose (Lack of margin for 360 mg/day dose for Contrave). Therefore, a systematic evaluation of PK in patients with mild, moderate, and severe hepatic impairment will help in guiding better dosing decision for Contrave. Therefore, this PMR requires sponsor to characterize the systematic evaluation of PK in subjects with mild, moderate, and severe hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

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- Animal Efficacy Rule
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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This will be a single dose pharmacokinetic trial in subjects with varying degree of hepatic impairment.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 200063

Product Name:

CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release
Tablets

PMR/PMC Description: Conduct a single-dose pharmacokinetic trial in subjects with mild, moderate, and severe renal impairment. Include overweight and obese subjects in the trial population.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	September 2015
	Study/Trial Completion:	November 2016
	Final Report Submission:	August 2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Only patients with moderate and severe renal impairment will be affected by lack of this knowledge. Availability of this information will help in guiding better dosing decision for Contrave in this specific population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The purpose of this PMR is to identify an unexpected risk of increased or more severe serious adverse events in patients with renal impairment treated with Contrave, due to altered kinetics of the drug in these patients.

The effect of renal impairment on pharmacokinetics of bupropion and naltrexone from Contrave is not fully understood. In healthy subjects, the systemic exposure of metabolite is higher for hydroxybupropion (AUC based Metabolite-to-parent ratio of 12 at steady-state), threohydrobupropion (AUC based Metabolite-to-parent ratio of 4 at steady-state), and erythrohydrobupropion (AUC based Metabolite-to-parent ratio of 1 at steady-state). Similarly, for orally administered naltrexone systemic exposures of 6-beta naltrexol are higher than naltrexone (AUC based Metabolite-to-parent ratio of 30 at steady-state). Bupropion and metabolites as well as naltrexone and its metabolite are renally excreted. The current bupropion and naltrexone product labels indicate a potential for significant accumulation of bupropion/naltrexone and its metabolites in the presence of renal impairment, although to a different magnitude for each of these components. However, the information is limited from a quantitative perspective in precisely guiding the dosing across varying degree of renal impairment. Further, the risk of seizures with bupropion is increased for 400 mg daily dose (Lack of margin for 360 mg/day dose for Contrave). Therefore, a systematic evaluation of PK in patients with mild, moderate, and severe renal impairment will help in guiding better dosing decision for Contrave. This PMR requires sponsor to characterize the systematic evaluation of PK in subjects with mild, moderate, and severe renal impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be a single dose pharmacokinetic trial in subjects with varying degree of renal impairment.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 200063
Product Name: CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets

PMR/PMC Description: Conduct a drug-drug interaction clinical trial with organic cation transporter 2 (OCT2) substrate, such as metformin, to evaluate the *in vivo* potential of Contrave constituents (bupropion and naltrexone) to inhibit OCT2. The trial should test the single-dose pharmacokinetics of the organic cation transporter 2 (OCT2) substrate with and without co-administration of Contrave (preferably at steady-state after multiple doses).

PMR/PMC Schedule Milestones: Final Protocol Submission: September 2015
Study/Trial Completion: April 2016
Final Report Submission: January 2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical data supports safety for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The purpose of this PMR is to identify unexpected risk of increased or more severe serious adverse events in patients taking Contrave and an organic cation transporter 2 (OCT2) substrate, due to altered kinetics of the drug(s) in these patients. The trial will evaluate the *in vivo* potential of Contrave constituents (bupropion and naltrexone) to cause a DDI via inhibition of OCT2, which are responsible for renal clearance of other concomitantly used drugs.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The trial will potentially be a drug-drug interaction study with an organic cation transporter 2 substrate (such as metformin). The trial should test single dose pharmacokinetic of metformin with and without co-administration of Contrave (preferably at steady-state after multiple dose).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

JENNIFER R PIPPINS
09/10/2014

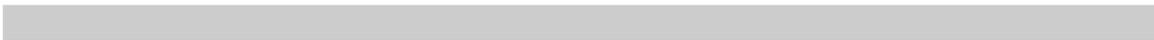
505(b)(2) ASSESSMENT

Application Information		
NDA #200063	NDA Supplement #: N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Contrave Established/Proper Name: naltrexone HCl / bupropion HCl Dosage Form: extended release tablets Strengths: 4 mg/90 mg and 8 mg/90 mg		
Applicant: Orexigen Therapeutics, Inc.		
Date of Receipt: March 31, 2010; Resubmission received on December 11, 2013		
PDUFA Goal Date: September 11, 2014	Action Goal Date (if different): 9/10/14	
Proposed Indication(s): Treatment of obesity and weight management, including weight loss and maintenance of weight loss.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Literature	Orexigen conducted a complete clinical development program (under IND 68,858) to support the evaluation of safety and efficacy of CONTRAVE, but did not conduct a preclinical development / animal toxicology program. Therefore, reliance on Agency findings and published literature for ReVia and Wellbutrin SR is primarily to support the preclinical safety of CONTRAVE. Of note, throughout the development program the clinical trial protocols consistently referred to ReVia and Wellbutrin SR prescribing information as an anchor for the known safety profiles of the two active drug substances comprising CONTRAVE.
Literature, "Antidepressant class labeling"	Labeling for Contrave

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The company did one bridging study (NB 230), comparing the relative bioavailability of approved forms of naltrexone IR and bupropion SR tablets to their tablet used for phase 3 studies. Contrave (naltrexone+bupropion) was compared to the naltrexone 50mg tablet from (b) (4) and bupropion SR 150mg tablet from (b) (4). Bioavailability was equivalent.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES × NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES x NO

If “**NO**”, proceed to question #5.
 If “**YES**”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
 YES X NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES × NO

*If “**NO**,” proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
ReVia® (naltrexone HCl)	NDA 18-932	Y
Wellbutrin SR® (bupropion HCl)	NDA 20-358	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A × YES NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer “**N/A**”.*

*If “**NO**”, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES NO X

*If “**YES**”, please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES NO X

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES NO X

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO X

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for new combination, new indication, dosage form and strength.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary,

that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO ×

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If “**YES**” to (c) **and** there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” **or** if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do **not** have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO ×

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

Wellbutrin SR: no unexpired patents

Revia: no patents listed

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph

III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

X 21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

PATRICIA J MADARA
09/10/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 29, 2014

To: Patricia Madara, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 200063
OPDP labeling comments for CONTRAVE® (naltrexone HCl and bupropion HCl) Extended-Release Tablets

OPDP has reviewed the proposed draft prescribing information (PI), medication guide, and carton/container labeling for CONTRAVE® (naltrexone HCl and bupropion HCl) Extended-Release Tablets (Contrave) that was submitted for consultation on March 10, 2014.

Prescribing Information and Medication Guide

OPDP has reviewed the proposed draft PI and medication guide (provided directly below) sent via email on August 27, 2014, by Patricia Madara (RPM).

OPDP notes that sections of the August 27, 2014, version of the draft Contrave PI are substantially similar to sections of the WELLBUTRIN SR (bupropion hydrochloride) Sustained-Release Tablets, for oral use (Wellbutrin SR) PI approved on July 17, 2014.

In addition, OPDP's comments regarding a previous version of the proposed draft medication guide were provided under separate cover in conjunction with the Division of Medical Policy Programs (DMPP) on May 14, 2014.

Carton/Container Labeling

OPDP has reviewed the proposed draft PI and has no further comments at this time.

Thank you for the opportunity to comment on the proposed draft labeling. If you have any questions, please contact Kendra Jones at 301.796.3917 or Kendra.jones@fda.hhs.gov.

49 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KENDRA Y JONES
08/29/2014

LABEL AND LABELING MEMO

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Memorandum: June 3, 2014
Requesting Office or Division: Division of Metabolism and Endocrinology
Application Type and Number: NDA 200063
Product Name and Strength: Contrave (naltrexone HCl and bupropion HCl) Extended-Release tablets, 8 mg/90 mg
Product Type: Multi-ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Orexigen Therapeutics, Inc
Submission Date: May 30, 2014
OSE RCM #: 2014-231-1
DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This memorandum evaluates the revised container labels and carton labeling for Contrave (naltrexone HCl and bupropion HCl) Extended-Release tablets, NDA 200063, submitted on May 30, 2014 for areas of vulnerability that could lead to medication errors. DMEPA previously reviewed the proposed labels and labeling under OSE Review #2014-231, dated March 11, 2014.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	N/A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	A
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed labels and labeling submitted on May 30, 2014 and noted that there are no concerns in terms of safety related to preventable medication errors. We compared the revised labels against the recommendations contained in OSE Review #2014-231, dated March 11, 2014 and determined that all of our comments were addressed.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling are adequate from a medication error perspective and therefore has no comments at this time.

If you have any further questions or need clarifications, please contact Terrolyn Thomas, OSE Regulatory Project Manager, at 240-402-3981.

APPENDIX A. PREVIOUS DMEPA REVIEWS

A.1 Methods

We searched an internal FDA database on June 3, 2014 using the term, Contrave to identify reviews previously performed by DMEPA.

A.2 Results

DMEPA previously reviewed the container labels, carton labeling, and prescribing information in OSE review #2014-231, dated March 11, 2014.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Contrave labels and labeling submitted by Orexigen Therapeutics on May 30, 2014.

- Container labels
- Carton labeling

B.2 Label and Labeling Images

Container Labels



¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MISHALE P MISTRY
06/03/2014

YELENA L MASLOV
06/04/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 15, 2014

TO: Eileen Craig, M.D., Clinical Reviewer
James P. Smith, M.D., Team Leader
Patricia Madara, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 200063

APPLICANT: Orexigen Therapeutics, Inc.

DRUG: Naltrexone HCl and bupropion HCl

NME: No

THERAPEUTIC CLASSIFICATION: This is a resubmission so there is a 6-month review clock.

INDICATIONS: For the treatment of obesity and weight management

CONSULTATION REQUEST DATE: January 31, 2014

CLINICAL INSPECTION SUMMARY GOAL DATE: May 19, 2014

DIVISION ACTION GOAL DATE: May 27, 2014

PDUFA DATE: June 10, 2014

I. BACKGROUND

The sponsor Orexigen Therapeutics, Inc. is seeking approval of Contrave[®] (32 mg naltrexone sustained-release (SR)/360 mg bupropion SR ([NB32]) Extended-Release Tablets for the treatment of obesity and weight management. The purpose of this resubmission is to address the approval deficiency noted in the Complete Response Letter (CRL) dated January 31, 2011. The application is based on the results of a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial, NB-CVOT (also referred to as XLA237) entitled “A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Occurrence of Major Adverse Cardiovascular Events (MACE) in Overweight and Obese Subjects With Cardiovascular Risk Factors Receiving Naltrexone SR/Bupropion SR”.

This is a multicenter study conducted in the United States. There are 266 sites that screened at least one subject and 264 sites that have at least one subject randomized to the treatment period. The first subject was screened June 1, 2012, and the cut-off date for the interim analysis was November 6, 2013. Overall, 13,192 subjects were screened for eligibility, 10,504 subjects were enrolled into the lead-in period and 8910 subjects were randomized into the 3-4 year treatment period. The treatment period is still ongoing.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 200063 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with this assignment.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol XLA237/ NB-CVOT # of Subjects Randomized	Inspection Date	Classification
Kevin Cannon Site #1151	136 subjects	March 24- April 3, 2014	NAI (preliminary)
Michael Noss Site # 1074	59 subjects	February 14-20, 2014	NAI
Margaret Rhee Site #1072	110 subjects	February 28, March 3-6, 2014	VAI

Bruce Rankin Site # 1033	51 subjects	February 19-21, 25, 2014	NAI
Rene Casanova Site #1020	23 subjects	April 8-25, 2014	VAI (preliminary)
Pharmaceutical Research Associates, Inc.		April 17, 21-24, 29-30; May 1, 6	VAI (preliminary)

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and/or review of EIR; final classification is pending letter to the site.

NOTE: During the inspection of all sites, it was noted that the worksheets/drug accountability logs provided by the sponsor and the training documents that are at the sites only address full, partial, and empty bottles returned for documenting drug accountability. (Full bottles contained 140 pills). The ClinPhone system that was used to document accountability electronically also only addresses full, partial, and empty bottles returned. The actual amount of test article returned in partial bottles is not being documented. The source documents for each visit (provided by the sponsor) have a space where the exact number of doses returned by the subject is being documented at each site.

In 21 CFR 312.57 it states: “A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment”.

The sponsor responded to inspectional questions with the following statement:

Given the purpose of this study was to assess safety (not efficacy) in a large number of subjects, it was deemed appropriate to address study drug reconciliation at the bottle level, i.e., counting returned bottles that were empty, partially full, or full. This is consistent with the risk-based approach taken in the overall monitoring of study conduct, and is described in the study protocol that was agreed to by the Agency (through a SPA) as well as approved by the IRBs. In order to ensure robust accountability, reconciliation is conducted at both the study site and at the returned drug depot (Almac).

Therefore, the FDA field investigators could not verify the quantity of study drug returned to the sponsor.

1. Kevin Cannon, M.D.
1907 Tradd Court
Wilmington, NC 28401

- a. **What was inspected:** The inspection included review of subjects' medical records, informed consents, laboratory results, case report forms, source documents, monitoring logs, drug accountability and data listings. In addition, the inspection also covered the regulatory binder and institutional review board (IRB) correspondences. There was full review of 34 subject records.
- b. **General observations/commentary:** There were 189 subjects screened and 136 randomized. The site enrolled its first subject in June 2012. There have been three onsite monitoring visits. The monitor has also been conducting monitoring calls and doing remote monitoring. The site is documenting the number of pills returned by the subjects at each visit and there were no discrepancies. The drug accountability log does not account for the number of pills being returned to the sponsor, only documenting full, partial or empty bottles.

A review of records did not reveal concerns related to data capture at this site. There was no under-reporting of adverse events. Primary efficacy endpoint data were verifiable. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

Although no FDA Form 483 was issued, items were discussed at the close out meeting or during the course of the inspection. These observations were related to SAEs being sent to the sponsor after the 24-hour required timeframe and all past medical history not on file during the screening phase.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Michael Noss, M.D.

11500 Northlake Drive
Suite 320
Cincinnati, OH 45249-1655

- a. **What was inspected:** The inspection consisted of review of IRB approval and correspondences, sponsor correspondences, monitoring records, informed consents, financial disclosure, investigators agreement, case report forms, temperature logs, and drug accountability. All data listings were verified with source documentation. A full record review was completed for 20 subjects. Informed consents and primary endpoint efficacy events were reviewed for all 59 subjects enrolled. All screen failures were reviewed.
- b. **General observations/commentary:** There were 86 subjects screened at this

site and 59 subjects randomized. All site personnel remain blinded to treatment. The IRB used was [REDACTED] (b) (6). A limited review of drug accountability was done as the study is still ongoing. No discrepancies were found. There was no under-reporting of adverse events. Primary efficacy endpoint data were verifiable. Subject 0077 had a cerebral vascular infarct on 09/01/2013. This was not listed on the data listing as it was reported after interim database locking. The site provided evidence that this was reported to the sponsor and was entered into the electronic case report forms.

A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued. However, there were three discussion items at close-out:

- A serious adverse event (SAE) for Subject 0064 was not reported to the sponsor within the required 24-hour time frame. The protocol states that all SAEs should be reported to the sponsor within 24 hours of the investigator being informed of the SAE. On [REDACTED] (b) (6), the subject's progress note states that she was hospitalized due to abdominal pain. The SAE report was not completed until 12/06/2013.
- A concomitant medication (Baclofen) for Subject 0073 was not listed on the data listing or in the firm's electronic data capture records.
- An October 2012 monitoring report was missing from the study files.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. Margaret Rhee, M.D.

530 South Main Street
Suite 1712
Akron, OH 44311

- a. **What was inspected:** Thirty six subject charts were reviewed. Source data related to eligibility, concomitant medications, adverse events, primary/secondary endpoints, deviations, randomization, and discontinuations were compared to the line listings and eCRFs. Also reviewed were IRB approvals and correspondences, 1572s, financial disclosure, training, curriculum vitae, delegation of duties, and drug accountability.
- b. **General observations/commentary:** Dr. Rhee was not the initial clinical investigator for the study. She was a sub-investigator in June 2012 and became the principal investigator on 9/11/2012. The study records were legible, organized and complete. Dr. Rhee reviewed the study data in a timely manner. All site personnel remain blinded to treatment. The IRB used was [REDACTED] (b) (4).

(b) (4). Monitoring was initially performed by (b) (4), which conducted the site qualification visit and two monitoring visits. Monitoring was then contracted by the sponsor to (b) (4). Only one onsite monitoring visit was performed and documented by (b) (4). Another visit occurred with the sponsor to review records but this was not documented in the monitoring log. There were several off-site remote monitoring calls.

There were 126 subjects screened at this site and 110 subjects randomized. Eight [001, 002, 018, 040, 083, 086, 087, 094] of the 126 subjects that were screened were screen failures. All of the subjects that were screened signed consent forms before any study specific tests were performed. There were 118 subjects that entered into the lead-in period of the study. Eight [011, 038, 049, 059, 065, 076, 112, 118] of the 118 subjects that entered into the lead-in period were not randomized into the treatment period because they did not meet the entrance criteria of the study. The first subject that was consented on 6/7/2012 was a screen failure; the first randomized subject was consented on 6/8/2012. The last subject was consented at the site on 11/26/2012.

It was noted that there was no Subject #107 in the line listings or records. Site staff indicated that at the time that Subject #106 was being registered during their screening Visit 2, coordinators were working together because one was in training. Records showed that Subject #106 was registered twice by the coordinators in IVRS; the second time the subject was registered, the subject was assigned study subject #107. The double registration of Subject #106 was discovered during the subject's screening visit and study subject #107 was deleted from the system.

During assessment of drug accountability, it was noted that the worksheets/drug accountability logs provided by the sponsor and the training documents that are at the site only address full, partial, and empty bottles returned for documenting drug accountability. The Clinphone system that was used to document accountability electronically also only addresses full, partial, and empty bottles returned. The actual amount of test article returned in partial bottles is not being documented. The source documents for each visit (provided by the sponsor) have a space where the exact number of doses returned by the subject is being documented at the site. *(This was subsequently confirmed at the other sites which were inspected and with email confirmation that the drug depot (b) (6) is not doing pill counts on partially used bottles).*

There was no under-reporting of adverse events and the primary and secondary endpoints were verifiable. The SAEs seen at the site agreed with the line listings for the 36 subjects' charts reviewed with the exception of the following:

- Subject 020: The site became aware of and entered an SAE [bilateral inguinal hernia procedure] for Subject 020 on 1/4/2013. Records

showed that the site was instructed to remove the SAE from the e-CRF by the monitor. During a monitoring visit on 2/19/2014, the site was instructed to restore the SAE in the e-CRF. A note to file from the sponsor indicates that the SAE was restored in the e-CRF on 2/21/2014. The bilateral inguinal hernia SAE for Subject 020 was not included on the line listings as the change was after the data cut-off date.

- Subject 080: The line listings indicate that the subject suffered from non-cardiac chest pains in 4/2013. The hospital discharge summary [dated (b) (6)] indicated that the subject was suffering from acute respiratory failure secondary to COPD. Site staff stated that the SAE was changed to acute respiratory failure secondary to COPD after review of all of the medical records.
- Subject 120: The subject's hospital discharge summary indicated that the subject was admitted to the hospital for a syncopal episode along with nonspecific colitis in (b) (6). Records showed that on 2/19/2014 (b) (4) requested that the SAE be changed from syncope to hospitalization for unstable angina. Dr. Rhee questioned the change and the decision not to change the SAE was made on 2/21/2014. This SAE was not listed on the line listing as it was past the interim cut-off date.

At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was issued as follows:

OBSERVATION 1

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically:

1. Subjects 020, 036 and 056 continued to take study medications despite having met the treatment discontinuation criteria of the study at Visit 6 (Week 16) of the study.
 - i. Visit 6 (Week 16) for Subject 020 was on 10/25/2012; treatment was stopped on 4/5/2013.
 - ii. Visit 6 (Week 16) for Subject 036 was on 11/1/2012; treatment was stopped on 4/5/2013.
 - iii. Visit 6 (Week 16) for Subject 056 was on 11/12/2012; treatment was stopped on 12/24/2012.

OSI comment: Subjects were to be discontinued at Visit 6 if they did not achieve a minimum weight loss of $\geq 2\%$ relative to baseline or had confirmed sustained blood pressure (systolic or diastolic) increased of ≥ 10 mmHg. All subjects met these criteria. Subject 020 had baseline blood pressure of 117/59 mmHg and Visit 6 reading of 141/73 mmHg. Subject 036 had a baseline blood pressure of 95/60 mmHg and a Visit 6 blood pressure reading of 113/60 mmHg. Subject 056 had baseline weight of 135.9 kg and a Visit 6 weight of 133.5 kg.

The PI responded to the 483 observation and acknowledged that these were oversights. A standard tool was not provided to calculate the weight change. For

Subject 056, study staff miscalculated. This was caught during a data query. The deviations were reported to the sponsor and IRB. Corrective actions have been taken. An update to the Visit 5 worksheet was made that requires the weight loss goal for Visit 6 to be calculated and entered into the source worksheet. This revision also includes the calculation to be used (weight in kg x 0.98). Source blood pressure logs now require an investigator to initial and date their review of the blood pressure against the termination criteria. All study staff were also re-educated on all protocol criteria during a staff meeting on March 11, 2014.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. **Bruce Rankin, D.O.**
860 Peachwood Drive
Deland, FL 32720

- a. **What was inspected:** Twenty four study charts were reviewed. Also reviewed were correspondence files, IRB approvals, training records, 1572s, financial disclosure, qualifications, delegation of duties, monitoring drug storage, and drug accountability records.
- b. **General observations/commentary:** There were 65 subjects screened and 51 subjects randomized. The site received one subject (#10370008) who was screened/consented at another site location; the subject switched from another site location. Therefore, there were a total of 66 subject charts for this study. This subject chart did not include a signed ICF Addendum, dated 1/28/13 (approved on 2/6/13). The IRB used was (b) (4). Monitoring was performed by (b) (4). Site initiation was 5/25/2102.

The study endpoints were verifiable based on documentation of suspected MACE in subject charts. One study endpoint was noted (Subject #10330038). During the inspection, another potential MACE for Subject #10330037 was being evaluated (SAE of unstable angina requiring hospitalization).

Two subjects (10330024 and 10330062) exhibited exclusion criterion 12, screening positive for benzodiazepines “if abuse or dependence is suspected”. Subject #10330024 was taking Temazepam and Subject #10330062 was taking Xanax. However, the sponsor provided the site with a waiver through emails and newsletter communication in order for the subjects to continue the study procedures.

There was no under-reporting of adverse events. Thirty-five subjects

experienced an adverse event and there were five SAEs. All SAEs were reported to the sponsor. There was one instance of AE severity for Subject #10330026 documented as mild, and reported in the eCRF as moderate. This was immediately sent for correction. There were also minor record filing discrepancies (IRB submission documents filed in the wrong chart, no investigator initials and date on two AE source documents, and correspondence documents about another study was filed with this study's records).

A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued. The minor issues noted above were discussed with the PI and study staff during the inspection and at the close-out meeting.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

5. Rene Casanova, M.D.

4401 North Andrew Avenue
Oakland Park, FL 33309

- a. **What was inspected:** The inspection consisted of review of IRB approval and correspondences, sponsor correspondences, monitoring records, informed consents, financial disclosure, 1572s, case report forms, and drug accountability. There were 20 subject records reviewed.
- b. **General observations/commentary:** There were 46 subjects screened and 23 subjects enrolled. There was no under-reporting of adverse events. The primary endpoint was verifiable. There were three SAEs at the site, (b) (4) a fatal myocardial infarction. There was a delay in reporting two of the SAEs to the sponsor. *There was also noted to be delayed signing of an informed consent addendum at this site discovered at the inspection of the contract research organization (b) (4) which was not reported by the FDA field investigator regarding this site.

At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was issued as follows:

OBSERVATION 1

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically:

- A. The Clinical Investigator's site was notified of an SAE on 11/28/12 for Subject #05. This subject experienced renal stones requiring

- hospitalization from (b) (6). This SAE was not reported to the sponsor until 5/7/13.
- B. The Clinical Investigator’s site was notified of an SAE on 2/25/13 for Subject #47. This subject experienced arterial occlusive disease and was hospitalized on (b) (6). The SAE was not reported to the sponsor until 4/24/13.
 - C. Two subjects out of nineteen reviewed had concomitant medications documented in their source records that were not documented in their electronic case report forms. For Subject #19 and subject #21, the only concomitant medications recorded in the electronic case report form were those that were obtained at their screening visits. These subjects had additional concomitant medications in their source documents that were not captured in the eCRFs.

OSI comment: The PI responded to the observations and acknowledged the late reporting of the SAEs. These deviations were reported to the IRB. The PI is updating his procedures as of 5/9/2014 to establish mandatory weekly meetings in order to review any and all recent SAEs and protocol deviations. As for the concomitant medications that were not sufficiently updated in the electronic database, the data entry position was dissolved and such responsibilities are not delegated to all study coordinators. Once these deviations were discovered, review of all source data from all subjects was done to ensure that all concomitant medications were entered appropriately.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

6. (b) (4)

- a. **What was inspected:** Transfer of obligations, contracts, SOPs, training, qualifications, data collection and transfer, drug accountability, and monitoring were reviewed. Also reviewed was adverse event reporting from all five sites inspected.
- b. **General observations/commentary:** (b) (4) is contracted for study conduct and monitoring currently. (b) (4) had previously been contracted to do the same. The Trial Master File is currently located at (b) (4). Transfer of obligations was in place. (b) (4) did not have any role in site selection as all sites were up and running prior to (b) (4) taking over. (b) (4) did not have any role in selection of the Data Monitoring Committee (DMC) members, any report writing, or maintenance of

the firewall. (b) (4) does not have access to unblinded data as they are not listed as having access per the Data Access Plan.

The sponsor maintained adequate oversight of the CRO and the clinical trial. Steps were taken to bring noncompliant sites into compliance. Financial disclosure information was obtained from each investigator and subinvestigator who was/is directly involved in the treatment and/or evaluation of the study subjects.

As noted during the site inspections, (b) (4) has only been doing bottle level accountability of drug product, not a full pill count. There were few onsite monitoring visits with most of the monitoring being done remotely off-site.

At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was issued as follows:

OBSERVATION 1

Failure to ensure proper monitoring of the study. Specifically,

- a. The study has not been monitored with enough frequency and depth to assure informed consent forms are documented in full and maintained as required. Since your firm's involvement with NB-CVOT began on 11/1/12, adequate risk-based monitoring was not implemented in that only one in-person monitoring visit was conducted at Site 1020 on 1/10/2013. At that visit, you reviewed a sample of 15 out of approximately 46 ICFs and detected IRB-reportable problems in four ICFs, which is over 26% of the sample. No additional monitoring activities took place to determine how widespread those ICF errors were at the site.

On or about 2/7/13, (b) (6) notified Site 1020 that a new addendum to the ICF had been approved for all enrolled subjects. Despite knowing Site 1020's past ICFs were not adequately documented, only telephone discussion was used to ensure consenting was being performed and documented properly; no written documentation was ever reviewed. During phone calls on 2/28/13 and 4/12/13, the site reported no problems and said they were having patients sign the addendum. However, on 4/25/13, the site notified the IRB that it failed to have approximately 25% of its currently enrolled subjects sign the addendum at their next visit. Despite the problems discovered in the initial ICF sample, and then the contradictory information regarding the addendums provided by the site on the phone calls, no site visit or document review took place to ensure the addendums were properly signed and documented.

- b. Monitoring was performed by individuals who were not fully trained. Review of seven employee training records reveal that all seven had not

fulfilled each of their training requirements before performing related tasks on the study.

Of the seven records sampled, four employees were contract research associates (CRAs) who perform onsite interim monitoring visits (IMVs).

CRA (b) (6) performed IMVs on and after 11/13/12 prior to documented completion of approximately:

- 1 out of 10 IMV-related, required project-specific trainings
- 9 out of 23 required core CRA trainings
- 11 out of 11 required SOP trainings

CRA (b) (6) performed IMVs on and after 11/7/12 prior to documented completion of approximately:

- 2 out of 10 IMVC-related, required project-specific trainings
- 3 out of 25 required core CRA trainings

CRA (b) (6) performed IMVs on and after 11/6/12 prior to documented completion of approximately:

- 1 out of 10 IMVC-related, required project-specific trainings

CRA (b) (6) performed IMVs on and after 11/13/12 prior to documented completion of approximately:

- 1 out of 10 IMVC-related, required project-specific trainings

Of the seven records sampled, three employees were site management associates who perform a monitoring function by conducting site management calls (SMCs) by telephone:

SMA (b) (6) performed SMCs on and after 2/20/13 prior to documented completion of approximately:

- 11 out of 16 SMC-related, required project-specific trainings
- 5 out of 27 required related SOP trainings
- 5 out of 37 required core SMA trainings

SMA (b) (6) performed SMCs on and after 1/16/13 prior to documented completion of approximately:

- 3 out of 16 SMC-related, required project-specific trainings

SMA (b) (6) performed SMCs on and after 12/17/13 prior to documented completion of approximately:

- 3 out of 16 SMC-related, required project-specific trainings
- 1 out of 27 required related SOP trainings

- c. Upon accepting monitoring responsibilities for a study that was already in-progress, you performed monitoring visits beginning on 11/6/12, prior

to having approved plans in place, including:

- The Clinical Management Plan (CMP), which defines how monitoring will occur, approved on 12/6/12
- The Transition Plan, approved by (b) (4) on 11/12/12.

Additionally, Document Control SOP MGTADM 002 G prohibits distributing unapproved documents, but copies of an unapproved draft version of the CMP were distributed to your CRAs on 11/1/12.

OSI comment: The inspection of the firm has recently ended and a response by the firm to the 483 observations has not yet been received.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Although regulatory violations were noted as described above, the audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of five domestic clinical sites as well as the contract research organization.

Drs. Cannon, Noss and Rankin were not issued a Form FDA 483; the classifications are all NAI (No Action Indicated). Data from these sites are considered reliable based on the available information and support validity of data as reported by the sponsor under this NDA.

Drs. Rhee and Casanova and (b) (4) were each issued a Form FDA 483 citing inspectional observations and classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data in support of this application may be considered reliable based on available information.

Observations noted above for Drs. Noss, Rankin and Rhee are based on the review of the Establishment Inspection Reports. Observations noted above for Drs. Cannon and Casanova and the contract research organization (b) (4) are based on review of the Form FDA 483s and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

Office of Scientific Investigations

CONCURRENCE:

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/s/

CYNTHIA F KLEPPINGER
05/15/2014

JANICE K POHLMAN
05/15/2014

KASSA AYALEW
05/15/2014

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

Provision of Pharmacovigilance Data

Date: May 15, 2014

Reviewer: Christine E. Chamberlain, PharmD, CDE, Safety Evaluator
Division of Pharmacovigilance I (DPV)

Team Leader: S. Christopher Jones, PharmD, MS, MPH, SE Team Leader

Product Name: Bupropion/Naltrexone (Contrave)

Subject: FAERS review of renal adverse events and potential new safety signals

Application Type/Number: NDA 200063

Applicant/Sponsor: Orexigen Therapeutics

OSE RCM #: 2014-964

1 INTRODUCTION

On May 2, 2014 the Division of Metabolic and Endocrine Products (DMEP) requested that the Division of Pharmacovigilance (DPV) query FAERS for bupropion reports coded with MedDRA terms related to renal adverse events, frequently reported events, and any other potential new drug safety signals. DPV completed a review in 2010 which characterized serious AERS reports associated with bupropion and naltrexone use in combination and as single agents.^a

DMEP requests this current information as background knowledge in support of a resubmission review for Contrave (bupropion/naltrexone) NDA 200-063. The sponsor, Orexigen Therapeutics, is seeking approval for the chronic treatment of obesity. This data provision provides crude data for adverse events reported in FAERS for bupropion, naltrexone and concomitant use of both agents, with a specific search for evidence of renal toxicity as a new drug safety signal. Bupropion and naltrexone are currently marketed as approved drugs under different names, but not in combination.

2 METHODS

2.1 FAERS SEARCH STRATEGY

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Tables 1, 2, and 3.^b

Table 1. FAERS Search Strategy to Identify Bupropion Reports	
Date of search	May 7, 2014
Time period of search	December 1, 1985* - May 7, 2014
Query Type	Quick Query
Product Terms (Suspect)	Bupropion, Bupropion Hydrobromide, Bupropion Hydrochloride
MedDRA Search Terms	All PT terms
Outcome	Serious
Case Type	Direct, 15-Day

* U.S. approval date for first bupropion NDA

Table 2. FAERS Search Strategy to Identify Naltrexone Reports	
Date of search	May 7, 2014
Time period of search	November 20, 1984* - May 7, 2014
Query Type	Profile
Product Terms (Suspect)	Naltrexone, Naltrexone hydrochloride
MedDRA Search Terms	All PT terms

^a Wyeth, J. Bupropion/Naltrexone (Contrave) AERS Review. OSE RCM # 2010-926. 17 August 2010.

^b FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population. FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

Table 3. FAERS Search Strategy to Identify Bupropion and Naltrexone Concomitant Use Reports	
Date of search	May 7, 2014
Time period of search	December 1, 1985* - May 7, 2014
Product Terms (Suspect)	Bupropion, Bupropion Hydrochloride, Naltrexone, Naltrexone hydrochloride
Query Type	Drug Interaction Quick Query
MedDRA Search Terms	All PT terms

2.2 EMPIRICA SIGNAL SEARCH STRATEGY

The Empirica Signal database was searched with the strategy described in Table 4.^c

Table 4. Data Mining Search Strategy	
Data Refresh Date	April 18, 2014
Product Terms	Bupropion, Bupropion Extended Release, Bupropion Slow Release Naltrexone
Empirica Signal Run Name	Generic (S)
MedDRA Search Strategy	HLTs: Renal failure and impairment Renal function analysis, Renal vascular and ischemic conditions Separate search of all PTs for each drug
Separate Search for Drug Interactions	
Empirica Signal Run Name	Generic 3D (S+C)
MedDRA Search Strategy	All PT terms

3 DATA

3.1 BUPROPION

We limited FAERS reports to reports without the terms “litigation” or “lawyer” in the narrative. The search strategy in Table 1 identified 14,722 crude count reports (may contain duplicates). The top 25 most frequently reported serious adverse events are listed in Table 5 and are consistent with current bupropion labeling. Stimulated reporting associated with

^c OSE uses Empirica Signal software, which uses the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm, to perform analyses on FAERS data and identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data.

communications and issuance of a boxed warning for suicidal thoughts and behaviors and neuropsychiatric reactions occurred during the time period of our search.

Table 5. The 25 Most Frequently Reported MedDRA Preferred Terms (PT) for Bupropion Products (n=14,722)		
Preferred Term	Count Of Events	Percent Of Total Cases
Completed suicide	2116	14.37%
Convulsion	1386	9.41%
Depression	1081	7.34%
Overdose	912	6.19%
Anxiety	757	5.14%
Suicidal ideation	752	5.11%
Toxicity to various agents	678	4.61%
Insomnia	677	4.60%
Drug ineffective	667	4.53%
Dizziness	642	4.36%
Drug interaction	640	4.35%
Headache	637	4.33%
Tremor	637	4.33%
Grand mal convulsion	634	4.31%
Agitation	609	4.14%
Intentional overdose	596	4.05%
Cardiac arrest	592	4.02%
Nausea	587	3.99%
Suicide attempt	527	3.58%
Confusional state	523	3.55%
Vomiting	463	3.14%
Poisoning	460	3.12%
Feeling abnormal	456	3.10%
Death	435	2.95%
Loss of consciousness	432	2.93%

3.2 NALTREXONE

Using the search strategy in Table 2, we retrieved 1,764 reports of which 1,074 were serious and 690 were non-serious. Table 6 lists the 25 most frequently reported adverse events with naltrexone and are consistent information conveyed with current labeling.

Table 6. The 25 Most Frequently Reported MedDRA Preferred Terms (PT) For Naltrexone (n=1,764)		
Event-Preferred Terms(PTs)	Total Cases	Percent of Total
Nausea	139	11.29
Vomiting	137	11.13

Drug withdrawal syndrome	124	10.07
Drug ineffective	113	9.18
Headache	101	8.20
Diarrhoea	90	7.31
Death	78	6.34
Drug interaction	77	6.26
Abdominal pain	70	5.69
Insomnia	68	5.52
Dizziness	67	5.44
Hyperhidrosis	66	5.36
Anxiety	62	5.04
Asthenia	61	4.96
Overdose	61	4.96
Agitation	59	4.79
Pain	58	4.71
Confusional state	55	4.46
Depression	54	4.39
Tremor	52	4.22
Malaise	51	4.14
Drug dependence	47	3.82
Injection site pain	45	3.66
Pruritus	41	3.33
Convulsion	40	3.25

3.3 BUPROPION AND NALTREXONE CONCOMITANT USE

The search strategy in Table 3 identified 66 reports with concomitant use of bupropion and naltrexone of which 40 were serious and 26 were nonserious. The 25 most frequently reported adverse events are listed in Table 7.

Table 7. The 25 Most Frequently Reported MedDRA Preferred Terms (PT) Reported with Concomitant Bupropion and Naltrexone (n=66 reports)		
Event-Preferred Terms(PTs)	Total Cases	Percent of Total
Anxiety	5	11.11
Arthralgia	5	11.11
Fall	5	11.11
Memory impairment	5	11.11
Nausea	5	11.11
Asthenia	4	8.89
Decreased appetite	4	8.89
Depression	4	8.89
Dizziness	4	8.89
Drug ineffective	4	8.89

Dyspnoea	4	8.89
Fatigue	4	8.89
Gait disturbance	4	8.89
Injection site pain	4	8.89
Injury	4	8.89
Paraesthesia	4	8.89
Suicidal ideation	4	8.89
Tinnitus	4	8.89
Vomiting	4	8.89
Weight increased	4	8.89
Agitation	3	6.67
Amnesia	3	6.67
Back pain	3	6.67
Chest pain	3	6.67
Diarrhoea	3	6.67

3.4 DATA MINING RESULTS

3.4.1 Data Mining Two Dimensional Analysis

Data mining results for bupropion and renal related events, by MedDRA Preferred Terms and High Level Terms (sorted by descending number of reports) are listed in Table 8. We found no disproportionality in reporting of renal related adverse events for bupropion using a standard DPV established threshold of $EB05 \geq 2$. All bupropion associated renal events are reported at a frequency that is less than expected using all other drugs in FAERS as a comparator.

Additionally, we looked at disproportionality of reporting for all adverse events reported with bupropion or naltrexone individually, and we did not identify any potential new signals with either drug.

Table 8. Data Mining Results* with greater than two reports for bupropion and renal related adverse events, by MedDRA Preferred Terms and High Level Terms (sorted by Descending Report numbers)

Generic name	PT	HLT	N	EBGM	EB05	EB95
Bupropion	Renal failure	Renal failure and impairment	61	0.298	0.241	0.366
Bupropion	Blood creatinine increased	Renal function analyses	57	0.384	0.307	0.474
Bupropion	Renal failure acute	Renal failure and impairment	54	0.32	0.255	0.398
Bupropion	Blood urea increased	Renal function analyses	27	0.383	0.277	0.519
Bupropion	Renal impairment	Renal failure and impairment	24	0.226	0.16	0.311
Bupropion	Oliguria	Renal failure and impairment	13	0.476	0.298	0.73

Bupropion	Renal tubular necrosis	Renal vascular and ischaemic conditions	9	0.409	0.233	0.677
Bupropion Slow Release	Renal failure	Renal failure and impairment	7	0.218	0.116	0.384
Bupropion	Blood creatine increased	Renal function analyses	6	0.542	0.273	0.989
Bupropion Slow Release	Blood creatinine increased	Renal function analyses	5	0.232	0.11	0.445
Bupropion Extended Release	Renal failure	Renal failure and impairment	5	0.081	0.038	0.155
Bupropion	Renal failure chronic	Renal failure and impairment	4	0.189	0.082	0.385
Bupropion Extended Release	Blood creatinine increased	Renal function analyses	4	0.114	0.049	0.232
Bupropion Extended Release	Renal failure acute	Renal failure and impairment	4	0.08	0.035	0.162
Bupropion	Blood creatinine abnormal	Renal function analyses	3	0.847	0.327	1.883
Bupropion Extended Release	Blood creatine increased	Renal function analyses	3	0.836	0.322	1.857
Bupropion	Blood creatinine decreased	Renal function analyses	3	0.716	0.276	1.591
Bupropion Slow Release	Blood urea increased	Renal function analyses	3	0.308	0.119	0.684
Bupropion Extended Release	Blood urea increased	Renal function analyses	3	0.213	0.082	0.473
Bupropion Extended Release	Renal impairment	Renal failure and impairment	3	0.144	0.056	0.32
Bupropion	Anuria	Renal failure and impairment	3	0.142	0.055	0.316
Bupropion Slow Release	Renal failure acute	Renal failure and impairment	3	0.119	0.046	0.264
Bupropion Extended Release	Glomerular filtration rate decreased	Renal function analyses	2	0.923	0.296	2.334

Bupropion	Blood urea	Renal function analyses	2	0.849	0.272	2.146
Bupropion	Blood creatinine	Renal function analyses	2	0.736	0.236	1.859
Bupropion Extended Release	Renal tubular necrosis	Renal vascular and ischaemic conditions	2	0.351	0.112	0.886

* Data mining scores do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

3.4.2 Data Mining Three Dimensional Analysis

We used Empirica Signal search strategy in Table 4 to identify a potential interaction with concomitantly administered bupropion and naltrexone using the Interaction Signal Score (INTSS), which is a relative measure of excess disproportionality present in the three-dimensional combination of two drugs and one adverse event term. An INTSS >1 indicates the confidence interval (CI) for the three-dimensional analysis is larger than expected and does not overlap the CI from the highest two component combination (drug-drug, drug-event). In Table 9 only memory impairment yielded an INTSS of >1. We note this score is very close to one and could represent an adverse effect of bupropion therapy or a symptom of clinical depression^d for which the drug is used to treat.

Generic name 1	Generic name 2	PT	SOC	N	INTSS
Bupropion	Naltrexone	Memory impairment	Nerv	5	1.012
Bupropion	Naltrexone	Nausea	Gastr	5	0.626

4 CONCLUSION

The data included in this memo is aggregated and crude, meaning that we have not reviewed individual case reports to assess any reported adverse event. Many of these reports are likely to be duplicates, and have substantial missing information that is inherent with any spontaneous reporting system.

We make no recommendations from these data. However, after reviewing frequently reported FAERS terms and disproportionality statistics for bupropion, naltrexone and the drugs in combination, DPV does not appreciate a signal for renal toxicity needing further review. After this cursory look, DPV also did not detect new safety signals attributed to either of these drugs individually or in combination.

^d Lyness JM. Unipolar depression in adults: Clinical features. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on May 12, 2014.)

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/s/

CHRISTINE E CHAMBERLAIN
05/15/2014

STEVEN C JONES
05/15/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 14, 2014

To: Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Kendra Y. Jones
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): CONTRAVE (naltrexone HCl and bupropion HCl)

Dosage Form and Route: Extended-Release Tablets, for oral use

Application Type/Number: NDA 200063

Applicant: Orexigen Therapeutics, Inc.

1 INTRODUCTION

On March 31, 2010, Orexigen Therapeutics Inc., submitted for the Agency's review a New Drug Application (NDA 200063) for CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets indicated for the treatment of obesity and weight management. On January 31, 2011, the Agency issued a Complete Response (CR) Letter sighting statistical deficiencies.

On December 10, 2013, Orexigen Therapeutics Inc., submitted for the Agency's review a Complete Response to the Complete Response (CR) Letter issued by the Agency on January 31, 2011 for CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on March 10, 2014, and March 10, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets.

2 MATERIAL REVIEWED

- Draft CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets MG received on December 11, 2013 and received by DMPP on May 07, 2014.
- Draft CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets MG received on December 11, 2013 and received by OPDP on May 07, 2014.
- Draft CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets Prescribing Information (PI) received on December 11, 2013, revised by the Review Division throughout the review cycle, and received by DMPP May 07, 2014.
- Draft CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets Prescribing Information (PI) received on December 11, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on May 07, 2014.
- Approved VIVITROL (naltrexone for extended-release injectable suspension) comparator labeling dated July 29, 2013.
- Approved WELLBUTRIN SR (bupropion HCL) Sustained-Release Tablets comparator labeling dated July 01, 2009.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of

60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
05/14/2014

KENDRA Y JONES
05/14/2014

MELISSA I HULETT
05/14/2014

LASHAWN M GRIFFITHS
05/14/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 11, 2014

Requesting Office or Division: Division of Metabolism and Endocrinology (DMEP)

Application Type and Number: NDA 200063

Product Name and Strength: Contrave (naltrexone HCl and bupropion HCl) Extended-Release tablets, 8 mg/90 mg

Product Type: Combination product

Rx or OTC: Rx

Applicant/Sponsor Name: Orexigen Therapeutics, Inc

Submission Date: December 10, 2013

OSE RCM #: 2014-231

DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH

DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton labeling, and prescribing information for Contrave (naltrexone HCl and bupropion HCl) Extended-Release tablets, NDA 200063, for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed labels and labeling and determined that there are no significant concerns. Thus, usual recommendations on increasing readability and prominence of important information on the proposed labels and labeling will be made.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA:

- A. Dosage and Administration section in Highlights of Prescribing Information and Full Prescribing Information:

- a. Due to the complex dose escalation schedule, use a table format for Dosage and Administration information within the Highlights of Prescribing Information, similar to what is presented within Section 2.1 (Recommended Dosing) of the Full Prescribing Information, to enhance accessibility of information per Guidance: Labeling for Human Prescription Drug and Biological Products, February 2013.¹
- b. Delete the statement (b) (4)

appearing in section 2.1 (Recommended Dosing) immediately underneath the section heading. (b) (4)


4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

A. Container label

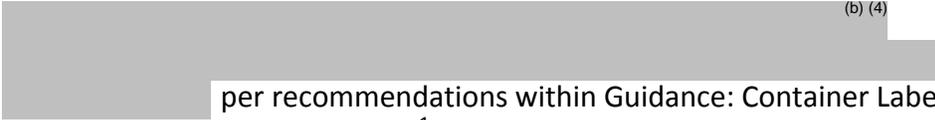
- a. The established name is ½ the size of the proprietary name, but lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
- b. The left section of the graphic design is larger than the proprietary name, established name, and product strength. Per Guidance: Container Labels and Carton Labeling, April 2013, remove or minimize the graphic design so that it does not compete in prominence with the proprietary name, established name, and product strength.²
- c. The product strength is located at the top of the label, separated from the proprietary name and established name. Relocate the product strength so that it is listed below the proprietary name, established name, and dosage form.

¹ Food and Drug Administration. *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements*, February 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf>.

² Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

- d. Although the net quantity statement appears away from the product strength, it competes for prominence because of the font size similar to the font size for the strength. Reduce the prominence of the net quantity statement by using smaller font size and consider relocating statement to the top of the label, based on section A.c.
- e. Increase the size and prominence of the warning statement, “Tablets should not be cut, chewed, or crushed” per Guidance: Container Labels and Carton Labeling, April 2013 as this is an important warning statement since manipulating the tablets by cutting, chewing, or crushing can increase the risk of seizures as specified in your package insert labeling.¹

B. Carton labeling

- a. See sections A.a through A.d.
- b. Orientation of Dose Escalation Instructions table is not oriented in the same direction and placed in the same field of vision as other text on the carton labeling. Relocate the Dose Escalation Instructions table to the back panel of carton labeling to allow for adequate space to orient text in same direction. Information currently located on the back panel can be relocated to panel where Dose Escalation Instructions are currently located.
- c.  (b) (4)
per recommendations within Guidance: Container Labels and Carton Labeling, April 2013.¹
- d. Include the warning statement, “Tablets should not be cut, chewed, or crushed”, on the carton labeling per Guidance: Container Labels and Carton Labeling, April 2013.¹

If you have further questions or need clarification, please contact Terrolyn Thomas, OSE Project Manager, at 240-402-3981.

¹ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Contrave that Orexigen Therapeutics submitted on December 10, 2013.

Table 2. Relevant Product Information for Contrave	
Active Ingredient	Naltrexone HCl and bupropion HCl
Indication	Management of obesity, including weight loss and maintenance of weight loss, in patients with an initial body mass index (BMI) of: <ul style="list-style-type: none">• 30 kg/m² or greater (obese)• 27 kg/m² or greater (overweight) in the presence of at least one weight-related co-morbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)
Route of Administration	Oral
Dosage Form	Extended-Release Tablets
Strength	8 mg naltrexone HCl/90 mg bupropion HCl
Dose and Frequency	Contrave dose escalation schedule: <ul style="list-style-type: none">• Week 1: One Contrave 8 mg/90 mg tablet daily in the morning• Week 2: Two Contrave 8 mg/90 mg tablets daily (one in the morning and one in the evening)• Week 3: Three Contrave 8 mg/90 mg tablets daily (two in the morning and one in the evening)• Week 4 (maintenance dose): Four Contrave 8 mg/90 mg tablets daily (two in the morning and two in the evening)
How Supplied	Supplied as an extended-release tri-layer tablet which are blue, round, bi-convex, film-coated, and debossed with "NB-890" on one side.
Storage	Store at 25°C (77°F); excursions permitted to 15° to 30 °C (59° to 86°F)
Container Closure	Opaque white high density polyethylene (HDPE) bottle, a ^{(b) (4)} cap with an induction seal, and an adsorbent packet.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁴ along with postmarket medication error data, we reviewed the following Contrave labels and labeling submitted by Orexigen Therapeutics on December 10, 2013.

- Container label
- Carton labeling
- Prescribing Information
- Medication Guide

B.2 Label and Labeling Images

Container Labels



⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MISHALE P MISTRY
03/11/2014

YELENA L MASLOV
03/11/2014

4/12/13



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 12, 2013

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Contrave (NDA 200063)
Indication: Treatment of obesity and weight management, including weight loss and maintenance of weight loss.
Dosages: naltrexone 8 mg and bupropion 90 mg, 4 tablets daily for a total daily dose of 32 mg naltrexone/360 mg bupropion (max dose)
Sponsor: Orexigen Therapeutics Inc.

Materials reviewed: Sponsor-provided meeting briefing document
Previous NDA review by Chad J. Reissig (CSS)

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II. DISCUSSION2

I. Summary

A. Background

The Division of Metabolism and Endocrinology Products (DMEP) consulted the Controlled Substance Staff (CSS) to review a meeting briefing document and attend a Type C, face-to-face meeting with the Sponsor on March 11, 2013. The Sponsor has one question for CSS:

“Can the Division confirm that sufficient information has been provided and that review by CSS has occurred to support that Contrave will not need post-approval scheduling assessments.”

B. Conclusions:

1. Overall, the abuse potential of Contrave does not warrant scheduling or control under the CSA at this time. However, new data included in the NDA resubmission (e.g. data from clinical trials examining the cardiovascular effects of Contrave) may affect this conclusion.
2. If Contrave is approved and post-marketing epidemiological data show evidence of misuse and abuse Contrave may be scheduled under the CSA at a later date.

C. Recommendations:

1. CSS has no further recommendations at this time.

II. Discussion

CSS previously reviewed Contrave on January 14, 2001. In the review, CSS noted that Contrave appears to have low potential for abuse, and does not require scheduling under the CSA. The Sponsor received a complete response (CR) letter on January 30, 2011. The CR letter noted that in phase 3 clinical trials, increases in blood pressure and heart rate were observed, along with adverse events (AEs) related to hypertension. The agency recommend the Sponsor conduct a randomized, double blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile.

Contrave (naltrexone and bupropion combination) is an orally administered combination product containing sustained release naltrexone and sustained release bupropion. The Sponsor is proposing two tablets of an 8/90 mg naltrexone/bupropion formulation for twice daily dosing (e.g., 16/32 mg of naltrexone/bupropion daily). FDA has previously reviewed both naltrexone and bupropion single entity products, and neither component is scheduled under the Controlled Substances Act (CSA). Both compounds have been evaluated in human and preclinical abuse potential studies and do not appear to demonstrate a potential for abuse.

NDA 200-063 is submitted under section 505 (b)(2) of the Food Drug and Cosmetic Act and relies upon previously collected safety data for the currently approved single entity naltrexone and bupropion products. For the abuse potential assessment of Contrave, the Sponsor has submitted a summary analysis of adverse events from completed clinical trials and abuse potential related information for the individual components from the public domain. CSS does not anticipate receipt of new information in the NDA resubmission that would affect the previous recommendation of non-controlled status. However, if analysis of AEs from the clinical trials recommended in the CR letter suggests a potential for abuse, scheduling under the CSA may be warranted. However, this possibility is unlikely.

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/s/

CHAD REISSIG
04/12/2013

SILVIA N CALDERON
04/12/2013

MICHAEL KLEIN
04/16/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 9, 2011

TO: File for Complaint #3232

FROM: Dan-My T. Chu, Ph.D.
Regulatory Review Officer
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance

THROUGH: Constance Cullity (formerly Lewin), M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance

SUBJECT: Complaint #3232
Amylin Pharmaceuticals
9630 Towne Centre Drive
San Diego, CA 92121

Orexigen Pharmaceuticals
3344 N. Torrey Pines Rd Ste 200
La Jolla, CA 92037

BACKGROUND:

On February 23, 2011, DSI was forwarded a complaint that was received by the Division of Metabolism and Endocrinology Products (DMEP). In a letter dated February 1, 2011, the complainant raised concerns about two pending NDAs based on knowledge that (b) (6)

Amylin Pharmaceuticals; investigational drug: Bydureon (exenatide LAR) [NDA 22,200]. The complainant alleged that the cardiac toxicity concerns raised by the FDA in the case of Bydureon were related to the (b) (6), (b) (4) that are incorporated into the investigational drug formulation. Specifically:

- The complainant stated that during her (b) (6), (b) (6), she was made aware of the firm's findings regarding the use of (b) (6), (b) (4). The complainant alleged that at the time, (b) (6) was investigating a (b) (6), (b) (4)

(b) (6), (b) (4). According to the complainant, the development of the investigational product was abandoned as preclinical toxicology testing uncovered evidence of potentially serious problems of cardiac toxicity and the possibility of stroke or myocardial infarct. The complainant stated that 3 toxicology reports were written by individuals at (b) (6) and the conclusion was that (b) (4)

(b) (4), (b) (6) into the venous system which might result in destruction of cardiac tissue, or cause myocardial infarct or stroke. The complainant noted that the author of the report determined that the causative agent of damage was most likely the (b) (6), (b) (4) and not the active ingredient. The complainant believed that the three reports were still retained by (b) (6).

- With regard to the Bydureon NDA, the complainant alleged that (b) (6)

(b) (6), (b) (4)
(b) (6)
(b) (6)
(b) (6)
The

(b) (6), (b) (4)
complainant alleged that in the case of Bydureon, the same (b) (6) investigated by (b) (6) was now incorporated into the formulation which could have bearing on the cardiac toxicity concerns with respect to the Amylin drug product.

Orexigen Pharmaceuticals, investigational drug Contrave (Naltrexone HCL and Bupropion HCL) [NDA 200.063]: The complainant alleged that the sponsor omitted safety data in a study with three treatment arms where the arm with the highest dose of bupropion (48 mg) had a very high drop-out rate due to side effects. (b) (6)

The complainant alleged that only the combination formulation with 48 mg bupropion showed continued weight loss after one year but as the side effects were so severe, the drop-out rate was high and the few subjects remaining in the 48 mg arm were unable to be analyzed for statistical significance. The complainant alleged that the decision was made to not include the data from the 48 mg arm and to limit the application for licensing to the two lower dosages.

COMPLAINT INVESTIGATION/EVALUATION:

Evaluation of Amylin Pharmaceuticals; investigational drug: Bydureon (exenatide LAR).

- Two clinical investigators were inspected with regard to NDA 22,200. Per the clinical inspection summary (CIS) dated December 29, 2009, data from the inspected sites were recommended as reliable in support of the application.
- In an email dated February 28, 2011, DSI reviewer Susan Leibenhaut was forwarded an assessment of the Bydureon complaint by the Pharm/Tox supervisor, Karen Davis Bruno. Dr. Bruno noted that she wasn't sure if the (b) (6), (b) (4) formulation used for Bydureon was the same as the (b) (6), (b) (4) formulation referred to by the complainant. Dr. Bruno noted that she did not see a compelling case for the cardiac toxicity for the (b) (6), (b) (4) in Bydureon as the amount of (b) (6), (b) (4) injected at each dose administration of Bydureon is ~30 times lower than that of other approved products containing (b) (6), (b) (4)

(b) (6), (b) (4). Dr. Bruno further noted that a literature review showed that there was no indication that (b) (6), (b) (4) or its degradation products cause systemic toxicity, reproductive or developmental effects, genotoxicity or carcinogenicity at clinically relevant doses.

- Review of the documentation in DAARTS shows that the sponsor was issued a complete response letter on March 12, 2010. Prior to the re-submission of a response by the sponsor on April 22, 2010, the FDA was made aware of a QT study (tQT) that took place between April and July 2008 as required by Health Canada. The FDA had not been informed of the study results or concerns raised by Health Canada. The sponsor was requested to submit the study results to FDA. Subsequent to the review of the study, in a letter dated October 18, 2010, DMEP sent the sponsor another complete response letter requesting the sponsor conduct an additional study to examine the safety of the drug and to also provide the results of another recently completed study. The sponsor disputed this complete response letter. In a letter dated May 11, 2011, the FDA informed the sponsor that their request for formal dispute resolution was denied.

The allegations made by the complainant were primarily related to the safety of the investigational drug product. Based on the review division's assessment by Dr. Bruno as discussed above, the allegations do not appear to raise any significant good clinical practice (GCP) concerns.

Evaluation of Orexigen Pharmaceuticals, investigational drug Contrave (Naltrexone HCL and Bupropion HCL):

- Five clinical investigators and the sponsor were inspected with regard to NDA 200,063. Per the clinical inspection summary (CIS) dated December 6, 2010, data from the clinical investigator sites were recommended as reliable in support of the application. The CIS reported preliminary information regarding the sponsor inspection and recommendations were made that the data reported in the NDA by the sponsor were considered reliable.
- Review of the documentation in DARRTS shows that the sponsor was issued a complete response letter on January 31, 2011.
- In emails dated February 23, 2011, DMEP medical officer, Dr. Eileen Craig provided information to DSI reviewers regarding her review of the complainant's letter. Specifically, Dr. Craig noted that:
 - o The complainant had the dosing confused as all the doses in the phase 3 studies used 360 mg bupropion and it was only the naltrexone dose (32 versus 48 mg) that was changed. Dr. Craig stated that the increase in naltrexone dose primarily caused the nausea and vomiting, and this information was submitted by the sponsor and reviewed by the FDA. Dr. Craig noted that there was also a phase 2 study that examined the combination 400 mg bupropion and 48 mg naltrexone dose that had a high drop-out rate primarily due to nausea and vomiting. There were ~61 subjects enrolled in that arm of the phase 2 study.
 - o The complainant's statement that the data from the higher dosage (48 mg) arm was omitted by the sponsor, was untrue. Dr. Craig noted that there were ~120 subjects randomized to the 360 mg bupropion/48 mg naltrexone arm. The review division had agreed to allow the ~120 subjects to be included in the safety analysis with the lower 32 mg naltrexone dosage group. The sponsor also provided narratives of SAEs and AEs that led to discontinuation of subjects on the higher 48 mg dosage and provided tables

- describing the safety data for the re-randomized arms.
- o While the complainant alleged that only the combination formulation with 48 mg bupropion showed continued weight loss after one year, this was not accurate as study NB303 was only one year in duration. In addition, the higher dosage of 360 mg bupropion/48 mg naltrexone dose did not show improved efficacy over the 360 mg bupropion/32 mg naltrexone dose in contrast to the complainant's statement.

The allegations made by the complainant that the safety data of the higher dosage was omitted by the sponsor, therefore, does not appear to be valid.

CONCLUSION:

No further DSI investigation of this complaint is warranted for the following reasons:

- With regard to the allegations made regarding Amylin Pharmaceuticals (investigational drug: Bydureon), the complaint was primarily related to issues regarding the safety of the investigational product. It was noted that a pharm/tox evaluation was conducted and did not find compelling evidence that the (b) (6), (b) (4) formulation used in the drug product was linked to cardiac toxicity. It is recommended that the review division follows its procedures for examining what additional safety evaluations, if any, will need to be investigated in lieu of the information provided by the complainant. There do not appear to be any GCP-related issues noted by the complainant with regard to Amylin's NDA 22,200.
- With regard to the allegations made regarding Orexigen Pharmaceuticals (investigational drug: Contrave), the medical officer's review appears to show that there was reporting of AEs of the higher dosage of study drug. Thus, the allegations do not appear to be valid.

{See appended electronic signature page}

Dan-My T. Chu, Ph.D.
Regulatory Review Officer
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Cullity (formerly Lewin), M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

DAN-MY T CHU
06/14/2011

CONSTANCE LEWIN
06/15/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****Pre-decisional Agency Information*****

Memorandum

Date: February 1, 2011

To: Meghna Jairath, Regulatory Project Manager,
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Jones, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Shefali Doshi, Acting Group Leader, DDMAC
Lisa Hubbard, Professional Group Leader, DDMAC
Samuel Skariah, Regulatory Review Officer

Subject: NDA 200063

DDMAC labeling comments for CONTRAVE[®] (naltrexone HCl and bupropion HCl) Extended-Release Tablets

We acknowledge receipt of your June 4, 2010, consult request for the proposed product labeling for CONTRAVE[®] (naltrexone HCl and bupropion HCl) Extended-Release Tablets, NDA 200063. Final labeling negotiations were not initiated during this review cycle and a Complete Response letter was issued on January 31, 2011. Therefore, DDMAC will provide comments regarding labeling for this application during a subsequent review cycle. DDMAC requests that DMEP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the Prescribing Information, please contact Samuel Skariah at 301.796.2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on Patient Labeling, please contact Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
02/01/2011



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 14, 2010

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Pharmacologist
Lori A. Love, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **Contrave (naltrexone and bupropion) SR tablets NDA 200-063**
Indication: Obesity
Dosages: naltrexone 8 mg and bupropion 90 mg (max. dose)
Sponsor: Orexigen Therapeutics Inc.

Materials reviewed: NDA submission located at: \\ [\CDSESUB1\EVSPROD\NDA200063](#)
Sponsor provided "Abuse Potential Assessment and Scheduling Recommendation"
Pubmed documents (see references)

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I. Summary

A. Background

This review responds to a consultation request from the Division of Metabolism and Endocrinology Products regarding the abuse potential of Contrave (NDA 200-063). Contrave (naltrexone and bupropion combination) is an orally administered combination

product containing sustained release naltrexone and sustained release bupropion. Both naltrexone and bupropion are marketed in the U.S. as single component pharmaceutical products. The Sponsor is proposing two naltrexone/bupropion formulations for marketing: a 4/90 mg naltrexone/bupropion formulation, and an 8/90 mg naltrexone/bupropion formulation. FDA has previously reviewed both naltrexone and bupropion, and neither component is scheduled under the Controlled Substances Act (CSA). Both compounds have been evaluated in human and preclinical abuse potential studies.

NDA 200-063 is submitted under section 505 (b)(2) of the Food Drug and Cosmetic Act and relies upon previously collected safety data for the currently approved single entity naltrexone and bupropion products. For the abuse potential assessment of Contrave, the Sponsor has submitted a summary analysis of adverse events from completed clinical trials and abuse potential related information for the individual components from the public domain (see: Sponsor provided “Abuse Potential Assessment and Scheduling Recommendation”).

B. Conclusions:

1. Overall, the abuse potential of Contrave does not warrant scheduling or control under the CSA at this time.
2. There are no data suggesting significant abuse potential related interactions between naltrexone and bupropion.
3. Naltrexone is not scheduled under the CSA, and does not have a significant abuse potential.
4. Bupropion is not scheduled under the CSA, and does not have a significant abuse potential.

C. Recommendations:

1. Contrave appears to have a low potential for abuse and does not require scheduling under the Controlled Substances Act.

II. Review

A. Drug Substances

For review purposes the individual components of Contrave are considered separately.

Naltrexone

Naltrexone is a mu opioid receptor antagonist. Its primary mechanism of action occurs by competitively binding to opioid receptors in the central nervous system (CNS). In the United States naltrexone is approved for the treatment of opioid addiction and alcoholism, and has also been used in opioid products to deter parenteral injection. Naltrexone is available in several preparations including, 50 mg tablets, a 380 mg/vial suspension for intramuscular injection, and a 12 mg/0.6 mL formulation for subcutaneous

injection. Although implantable forms of naltrexone have been created, none are approved for clinical use in the U.S.

Naltrexone does not have any known abuse potential in humans. Preclinical studies are also negative for signs of abuse potential.

Bupropion

Bupropion is an atypical antidepressant that functions primarily as a dopamine and norepinephrine reuptake inhibitor. In the United States, bupropion is approved for the treatment of major depression and available in several formulations including 50, 75, and 100 mg immediate release tablets, and a 522 mg extended release tablet.

Bupropion shares some structural, neurochemical, and behavioral properties of classic psychostimulants. Initially used as an antidepressant, bupropion has more recently been used as a smoking cessation agent (Fant et al. 2009; Frishman 2009).

Bupropion does not have a significant abuse potential and is not considered a drug of abuse. However, bupropion is unique because some preclinical studies are positive for abuse potential. Bupropion is self-administered by rats (Tella et al. 1997) and monkeys (Bergman et al. 1989; Lamb and Griffiths 1990). In drug discrimination studies, bupropion is able to substitute for the stimulus effects of cocaine, methamphetamine, and d-amphetamine (Kamien and Woolverton 1989; Katz et al. 2000; Lamb and Griffiths 1990; Munzar and Goldberg 2000). Bupropion also produces conditioned place preference in rodents, suggesting that it produces rewarding effects (Ortmann 1985).

Despite these preclinical findings, bupropion does not show abuse potential in clinical experimental assessments and there is no data on abuse associated with public health problems. In volunteers with a history of amphetamine abuse, 100, 200, and 400 mg of bupropion were not discriminated from placebo and liked less than 15 and 30 mg of dextroamphetamine (Griffith et al. 1983; Miller and Griffith 1983). In non-drug users, 50 and 100 mg of bupropion did not produce statistically significant changes on subjective effects measures, including subjective effects that may be indicative of abuse potential (Peck et al. 1979). In a group of 5 non-drug using volunteers trained to discriminate *d*-amphetamine (20 mg) from placebo, bupropion did not occasion more than 40% amphetamine-appropriate responding at any of the doses tested (50, 100, 200, 300, and 400 mg). While the highest dose of bupropion (400 mg) increased participant ratings of “alert-energetic”, “vigorous”, “elated”, and “good effects” to a significant degree, ratings of “like drug” after 400 mg of bupropion were not increased relative to placebo. Bupropion did increase scores on the placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), suggesting mild amphetamine-like effects (Rush et al. 1998). Drug Abuse Warning Network (DAWN) data show minimal abuse but some possible misuse of bupropion resulting in hospital emergency department visits (2004-2009).

In male smokers given the sustained released formulation of bupropion (bupropion-SR, 150 mg), or caffeine (178 mg) twice daily, cumulative visual analog scores for questions such as “high” and “pleasant” were not significantly increased (Zernig et al. 2004). Collectively, the human experimental data suggest a low abuse potential of bupropion despite the findings in animal studies.

Contrave

Contrave is a novel combination product for the treatment of obesity. Contrave will be available in two doses: a preparation containing 8 mg naltrexone and 90 mg bupropion (8/90) and a lower dose containing 4 mg naltrexone and 90 mg bupropion (4/90). The proposed daily dose is two tablets twice daily, taken orally for a total dose of 32 mg naltrexone/360 mg bupropion. Titration to the maximum dose will occur over a three week period.

1. Product description

Contrave is a fixed-dose combination compound of naltrexone sustained release (SR) and bupropion SR. Contrave is a trilayer tablet with two SR layers, one for each active pharmaceutical ingredient, that are physically separated by an inert layer. (b) (4)

2. Extended release formulations

The extended release properties of Contrave can be circumvented. Crushing a Contrave tablet would result in a more rapid release of both drug components. However, even if the extended release properties of Contrave were eliminated, the maximum dose of either individual drug would be less than currently available single entity IR formulations (e.g., naltrexone 50 mg IR tablet, bupropion 100 mg IR tablet).

B. Clinical Studies

The Sponsor has conducted 12 Phase 1 studies and two Phase 2 studies administering naltrexone and bupropion single entity products in combination. Four Phase 3 studies have been performed with the intended commercial product.

Study NB-230 compared the single-dose bioavailability of Contrave to commercially available single entity immediate release (IR) naltrexone and sustained release (SR) bupropion. Two tablets of Contrave were administered for a total dose of 16 mg naltrexone/180 mg bupropion. Single tablets of 50 mg IR naltrexone and 150 mg bupropion SR were used as comparators and administered simultaneously.

According to the Sponsor, the dose-adjusted C_{max} for the naltrexone component of Contrave was 44% lower than IR naltrexone. This is expected given the immediate release properties of the single entity naltrexone reference compound. Dose-adjusted plasma bupropion levels were comparable between the reference compound (bupropion SR 150 mg tablet) and Contrave.

The Sponsor feels that this study fulfills formal bioequivalence criteria for Contrave and the approved naltrexone and bupropion reference products.

During clinical trials, only one subject experienced a serious adverse event (SAE) from the group of abuse-related AE terms. A 56-year-old female experienced anxiety after receiving a dose of 32/360 naltrexone/bupropion. The event was classified as “moderate” in intensity and considered possibly related to the study drug. The subject was withdrawn from the study.

As part of the abuse potential assessment of Contrave, the Sponsor analyzed and searched treatment emergent adverse events (TEAS) for abuse-related terms. The Sponsor analyzed abuse-related AEs from Phase 2 and Phase 3 studies and performed a separate analysis of Phase 1 AEs. The incidence of abuse related AEs was not analyzed statistically.

In Phase 1 studies fatigue and somnolence were the most common abuse-related AEs observed. There was one report of euphoric mood in a subject that received a 37.5/270 mg dose of naltrexone/bupropion. The subject experienced euphoria approximately 24 hours after taking her first dose of the study drug. She took a second dose about 80 minutes after the initial onset of euphoria. The euphoria resolved after 6.5 hours. The event was coded as moderate and the relationship to the study drug was considered unlikely. Other CNS-related AEs from Phase 1 studies are shown in Table 1.

Table 2 shows abuse related and other CNS-related AEs from placebo controlled Phase 2 and Phase 3 studies. In all studies except placebo, bupropion was given at 360 mg. Only the dose of naltrexone differed across groups. The dose of naltrexone ranged from 16-48 mg.

In Phase 2 and Phase 3 studies, four subjects (0.1%) reported euphoric mood. All were receiving naltrexone 32 mg/bupropion 360 mg). An additional 3 subjects reported elevated mood. All events were classified as mild and no action was taken.

C. Integrated abuse potential assessment

1. Findings

Because this NDA is a 505b 2 application, the Sponsor has relied on previous safety findings from the published literature and the Agency’s previous findings of safety and effectiveness for the drug.

Contrave is a combination product containing naltrexone and bupropion. Neither naltrexone nor bupropion are scheduled under the CSA or are known to have a significant abuse potential. Based on the AE analysis from clinical studies, Contrave appears to have a low abuse potential that is similar to bupropion and naltrexone. Contrave does not require scheduling or control at this time.

Table 1. Abuse-related AEs from Phase 1 studies

Preferred Term	Treatment Group					
	N16/B180 n = 237	N8/B180 n = 20	NB/DDI n = 71	NB/OTH n = 59	NB/32 n = 18	Any NB n = 316
Euphoria-type abuse potential AEs						
Euphoric Mood	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (0.3%)
Other CNS-related AEs						
Fatigue	30 (12.7%)	0 (0.0%)	0 (0.0%)	2 (3.4%)	0 (0.0%)	32 (10.1%)
Somnolence	15 (6.3%)	0 (0.0%)	0 (0.0%)	7 (11.9%)	0 (0.0%)	22 (7.0%)
Nervousness	3 (1.3%)	0 (0.0%)	2 (2.8%)	0 (0.0%)	0 (0.0%)	5 (1.6%)
Agitation	2 (0.8%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	3 (1.0%)
Asthenia	2 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Paraesthesia	2 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Hypervigilance	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Lethargy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (0.3%)

N16/B180 = naltrexone 16mg/bupropion 180 mg

N8/B180 = naltrexone 8mg/bupropion 180 mg

NB/DDI = naltrexone 16mg/bupropion 180 mg in drug-drug interaction (DDI) studies.

NB/OTH = subjects dosed with naltrexone 37.5mg/bupropion 270 mg or naltrexone 36mg/bupropion 270 mg

NB32 = naltrexone 32mg/bupropion 360 mg

Any NB = any combination of naltrexone and bupropion

Table 2. Abuse-related AEs with an incidence of 0.5% or greater in Phase 2 and Phase 3 studies.

Preferred Term	Placebo n = 1515	NB16 n = 633	NB32 n = 2545	NB48 n = 61	NB ALL n = 3239
Euphoria-type abuse potential AEs					
Euphoric mood	0 (0.0%)	0 (0.0%)	4 (0.2%)	0 (0.0%)	4 (0.1%)
Elevated mood	0 (0.0%)	1 (0.2%)	2 (<0.1%)	0 (0.0%)	3 (<0.1%)
Other CNS-related AEs					
Fatigue	52 (3.4%)	27 (4.3%)	103 (4.0%)	0 (0.0%)	130 (4.0%)
Anxiety	43 (2.8%)	16 (2.5%)	108 (4.2%)	3 (4.9%)	127 (3.9%)
Somnolence	12 (0.8%)	9 (1.4%)	32 (1.3%)	1 (1.6%)	42 (1.3%)
Feeling Jittery	5 (0.3%)	3 (0.5%)	36 (1.4%)	2 (3.3%)	41 (1.3%)
Depression	23 (1.5%)	9 (1.4%)	24 (0.9%)	1 (1.6%)	34 (1.0%)
Lethargy	4 (0.3%)	5 (0.8%)	26 (1.0%)	0 (0.0%)	31 (1.0%)
Abnormal dreams	6 (0.4%)	4 (0.6%)	25 (1.0%)	0 (0.0%)	29 (0.9%)
Depressed mood	18 (1.2%)	2 (0.3%)	23 (0.9%)	0 (0.0%)	25 (0.8%)
Feeling abnormal	2 (0.1%)	3 (0.5%)	20 (0.8%)	1 (1.6%)	24 (0.7%)
Asthenia	1 (<0.1%)	3 (0.5%)	18 (0.7%)	0 (0.0%)	21 (0.6%)
Paraesthesia	9 (0.6%)	3 (0.5%)	17 (0.7%)	0 (0.0%)	20 (0.6%)
Hypoaesthesia	11 (0.7%)	5 (0.8%)	13 (0.5%)	0 (0.0%)	18 (0.6%)
Nervousness	2 (0.1%)	3 (0.5%)	13 (0.5%)	2 (3.3%)	18 (0.6%)

NB16 = naltrexone 16 mg/bupropion 360 mg

NB32 = naltrexone 32 mg/bupropion 360 mg

NB48 = naltrexone 48 mg/bupropion 360 mg

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/s/

CHAD REISSIG
01/14/2011

LORI A LOVE
01/14/2011

MICHAEL KLEIN
01/14/2011

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

Date: December 7, 2010

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products

Through: Melina Griffis RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Richard Abate, RPh, MS, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Contrave (Naltrexone HCl and Bupropion HCl) Extended-
release Tablets, 4 mg/90 mg and 8 mg/90 mg

Application
Type/Number: NDA 200063

Applicant: Orexigen Therapeutics, Inc.

OSE RCM #: 2010-1081

1 INTRODUCTION

This review provides comments from the Division of Medication Error Prevention and Analysis regarding potential medication error issues identified with the proposed container labels, carton and insert labeling for Contrave (NDA 200063) submitted by Orexigen Therapeutics, Inc on March 31, 2010. DMEPA found the proposed proprietary name included in these labels, Contrave, acceptable.

2 MATERIAL REVIEWED

Using Failure Mode and Effects Analysis, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the product labels and labeling submitted March 31, 2010 to identify vulnerabilities that may lead to medication errors. See Appendices A and B for samples of the draft container labels.

3 CONCLUSIONS AND RECOMMENDATIONS

Our Label and Labeling Risk Assessment indicates that the presentation of information on the label and labeling introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval, and thus we provide recommendations in the following sections that aim at reducing the risk of medication errors.

3.1 COMMENTS TO THE DIVISION

Our Label and Labeling Risk Assessment indicates that the presentation of information on the label and labeling introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval, and thus we provide recommendations in the following sections that aim at reducing the risk of medication errors. We request the recommendation in Section 3.1 be communicated to Orexigen Therapeutics prior to the approval of this NDA.

Please copy the Division of Medication Error Prevention and Analysis on any communication to Orexigen Therapeutics with regard to this review. If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

3.2 COMMENTS TO THE APPLICANT

A. General Comments

1. The presentation of the strength throughout the insert labeling requires the unit of measure (mg) for all active ingredients and should be presented as follows: (b) (4) 8 mg/90 mg.

B. Container labels (b) (4) 8 mg/90 mg tablets, 120 count)

1. (b) (4)
A 70 count container is appropriate for titration. (b) (4)
(b) (4) a

(b) (4)

If a 70 count container is developed for titration, we recommend including titration directions on the container (b) (4) label similar to the those included in the medication guide.

2. Revise and reduce the size of the graphic appearing above the proprietary name to provide more prominence to the proprietary and established names.
3. Established Name
 - i. Delete the “/” in the established name and replace it with the word “and.” For example, naltrexone HCl and bupropion HCl.
 - ii. Revise the presentation of the established name on the container labels so that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).
4. Relocate the strength presentation to appear directly below the established name.
5. Revise the presentation of the dosage form to increase the font size similar to the established name.
6. Revise the Attention statement to read “Attention Pharmacists: Dispense with Medication Guide.” Relocate this statement to the principle display panel to more prominently provide this important information.
7. Debold the RX only statement, and relocate it to the side panel.
8. (b) (4)
9. Relocate the “Each tablet contains...” statement to the side panel.
10. Relocate the net quantity so that it does not appear in the background color. Additionally, reduce the font size so that it is smaller and not as prominent compared to the strength presentation.
11. Revise to include a barcode as required by 21 CFR 201.25.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RICHARD A ABATE
12/07/2010

MELINA N GRIFFIS
12/07/2010

CAROL A HOLQUIST
12/07/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 6, 2010

TO: Meghna M. Jairath, Pharm.D, Regulatory Project Manager
Eileen Craig, Medical Officer
Division of Metabolic and Endocrine Drug Products

FROM: Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Jean Mulinde, M.D.
Team Leader/Acting-Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 200-063

APPLICANT: Orexigen Therapeutics, Inc.

DRUG: Contrave (naltrexone HCl and bupropion HCl) extended-release tablet

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: Treatment of obesity and weight management

INSPECTION SUMMARY GOAL DATE: January 1, 2010

PDUFA DATE: January 31, 2010

I. BACKGROUND: The applicant, Orexigen Therapeutics, Inc., submitted this New Drug Application for the use of a combination product, naltrexone sustained release (SR)/bupropion sustained release (NB), for the treatment of obesity and weight management. Naltrexone HCL is an approved mu-opioid antagonist indicated for the treatment of opiate and alcohol dependence, while bupropion HCl is an approved norepinephrine and dopamine reuptake

inhibitor indicated for the treatment of major depression and nicotine dependence. Bupropion is known to cause weight loss when used for its currently approved indications. It was hypothesized that use of the two drugs in combination could provide a unique therapeutic option for weight loss and management.

The efficacy, safety and tolerability of NB were evaluated in four pivotal Phase 3 studies: in obese subjects receiving customary diet and behavioral counseling (Studies NB-301 and NB-303), in obese subjects undergoing intensive lifestyle modification counseling (Study NB-302), and in obese subjects with type 2 diabetes (Study NB-304). In each of these studies, the efficacy of NB was to be established using the FDA recommended co-primary endpoints of:

1. The percent change from baseline in total body weight (LOCF) between the active drug treatment group and the placebo group
2. The percentage of subjects who achieved a weight loss of $\geq 5\%$ from baseline between the active drug treatment group and the placebo group

FDA conducted 5 PDUFA clinical investigator inspections for this NDA, and also conducted a sponsor inspection (Orexigen), to evaluate the sponsor's oversight of the studies submitted in the NDA.

The protocols inspected included:

NB 301: "A Multicenter, Randomized, Double Blind, Placebo Controlled Study Comparing the Safety and Efficacy of Two Doses of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Obese Subjects."

NB 302: "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained- Release (SR) and Placebo in Subjects with Obesity Participating in a Behavior Modification Program."

NB-303: "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained- Release (SR) and Placebo in Obese Subjects."

NB-304: "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone 32 mg Sustained Release (SR)/Bupropion 360 mg Sustained Release (SR) and Placebo in Obese Subjects with Type 2 Diabetes Mellitus."

II. RESULTS (by Site):

Name of CI, or Sponsor & Location	Site #, Protocol # and # of Subjects	Inspection Dates	Final Classification
Mark Graves, MD Deaconess Clinic Downtown 421 Chestnut Street Evansville, IN 47713	Site #86 Protocol NB-301 109 Subjects	July 7 – July 9, 2010	NAI
Carl Griffin, MD Lynn Health Science Institute 3555 NW 58 th St., Suite 800. Oklahoma City, OK 73112	Site #87 Protocol NB-301 44 subjects	June 28 - July 12, 2010	NAI
James Hill, MD Center for Human Nutrition 4200 East Ninth Avenue University of Colorado Health Services Center Denver, CO 80262	Site #28 Protocol NB-302 101 subjects	July 6 - July 10, 2010	Pending (Preliminary Classification VAI)
Douglas Young, MD Northern California Research 3840 Watt Ave; Bldg E Sacramento, CA 95821	Site #75 Protocol NB-303 72 subjects	June 29, 2010 – July 7, 2010	VAI
Philip Snell, MD Mountain View Clinical Research, Inc. 406 Memorial Drive Greer, SC 29651	Site #42 Protocol NB-304 9 subjects Protocol NB-303	June 24 – July 9, 2010	NAI
Orexigen Therapeutics, Inc. 3344 N. Torrey Pines Court, La Jolla, CA 92037	Sponsor	August 30- September 4, 2010	Pending (Preliminary Classification NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.**Rationale for Site Selections:**

For NB-301, Site #86 (Graves, 109 subjects) and Site #87 (Griffin, 86 subjects) enrolled the most number of subjects. Dr. Graves had 21 INDs in COMIS, with a prior NAI inspection in

May 2008. Dr. Griffin had 5 INDs in COMIS, with a prior NAI inspection in October 2008.

For NB-302, Site #28 (Hill) was the second highest enrolling site (101 subjects). Dr. Hill had 5 INDs in COMIS, and no prior inspections.

For **NB-303**, Site #75 (Young), was the 2nd highest enrolling site (79 subjects), and was listed with 160 INDs in COMIS and 3 prior inspections: May 2008 – VAI; April 2008 – VAI; July 2006 NAI.

For **NB-304**, Site #42 (Snell) was the 2nd highest enrolling site (19 subjects), and was listed in COMIS with 46 INDs, and no prior inspections.

1. Mark Graves

Deaconess Clinic
421 Chestnut Street
Evansville, Indiana 47713

a. What was inspected: Dr. Mark Graves conducted Study NB-301 – “A Multicenter, Randomized, Double-blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Two Doses of NB and Placebo in Obese Subjects.” At this site, 159 subjects were screened for the study, 50 subjects failed the study screening, 109 subjects were randomized, and 42 subjects either terminated early from the study or withdrew consent. A total of 67 subjects completed the study. No deaths or SAEs were reported at this site.

An audit of 83 subjects' records was conducted, which included records for 38 subjects that completed the study. In addition, the field investigator reviewed the informed consent forms for all 159 subjects screened, records for 20 early termination subjects, and records for 25 screen failure subjects. The following records were reviewed: adequacy of documentation; laboratory reports; key personnel responsibility log; inclusion and exclusion criteria; review and reporting of adverse events; concomitant medications; test article accountability records; IRB and sponsor correspondences; comparison of source documents with Case Report Forms (CRFs) and data listings from the sponsor, with respect to primary and secondary efficacy endpoints. There were no limitations to this inspection.

b. General observations/commentary: Source documents were compared with CRFs and the field investigator reported that no discrepancies were noted. Specifically, the field investigator reported: the primary and secondary efficacy endpoints were verifiable; adverse events were accurately reported; concomitant medications were accurately reported; source data and CRFs corroborated with the data listings provided by the sponsor. No regulatory violations were noted, and no Form FDA 438 was issued to Dr. Graves.

c. Assessment of data integrity: Based on review of the inspectional findings for Dr. Grave's site, the data generated by this site appear acceptable in support of the respective indication.

2. Carl Griffin, M.D.

Lynn Health Science Institute
3555 NW 58th St., Suite 800
Oklahoma City, OK 73112

a. **What was inspected:** Dr. Carl Griffin conducted Study NB-301—“A Multicenter, Randomized, Double-blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Two Doses of NB and Placebo in Obese Subjects.” At this site, 113 subjects were screened for the study, 50 subjects failed the study screening, 87 subjects were randomized, and 41 subjects either terminated early from the study or withdrew consent. A total of 42 subjects completed the study.

The field investigator reviewed the informed consent forms for all 113 subjects that were screened for the study; conducted an in-depth audit of 37 (of 42) records of subjects who completed the study; and reviewed records for 24 subjects who terminated early from the study. The audit consisted of the following: adequacy of documentation; laboratory reports; key personnel responsibility log; inclusion and exclusion criteria; reporting of adverse events; concomitant medications; protocol deviations; body weight and vitals; test article accountability records; reasons for discontinuations and withdrawals; IRB and sponsor correspondence; and monitoring logs. The inspector compared the data in the source documents with the data recorded on the CRF, with respect to primary and secondary efficacy endpoints.

b. **General observations/commentary:** The field investigator compared the data in source documents with the data documented on the CRF, and noted no discrepancies. The field investigator reported that the primary and secondary efficacy endpoints were verifiable; adverse events were accurately reported; concomitant medications were accurately reported; and the source data and CRFs corroborated with the data listings provided by the sponsor.

Although no Form FDA 438 was issued, the field investigator made several observations during the inspection that were discussed with Dr. Griffin at the close-out visit. These observations were related to the site’s need for due diligence in collecting information related to adverse events and concomitant medications, as the inspection noted that the site did not document vitamins, or concomitant medications taken during certain medical procedures, including anesthesia for one subject. Additionally, the field investigator noted a few instances where dates were incorrectly documented in progress notes. These discussion issues were not cited on a Form FDA 483, as they appeared to be isolated events, and were considered unlikely to significantly impact the efficacy and safety data generated by this site.

c. **Assessment of data integrity:** Although minor instances of documentation deficiencies

were noted, these are considered isolated in nature, and unlikely to significantly impact the reliability of primary safety and efficacy data from this site. Based on review of the inspectional findings for Dr. Griffin's site, the study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the respective indication.

3. James Hill, M.D.

Center for Human Nutrition
4200 East Ninth Avenue
University of Colorado Health Services Center, Room 300-Z
Denver, Colorado 80262

a. What was inspected: Dr. James Hill conducted Study NB 302: "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained- Release (SR) and Placebo in Subjects with Obesity Participating in a Behavior Modification Program. At this site, 182 subjects were screened, and 101 subjects enrolled. The field investigator reported that 75 subjects completed the study. For the inspection, the field investigator reviewed 31 records (of 75 subjects completing the study, 41%). Specific records reviewed included; adverse events; primary efficacy endpoints; protocol deviations; inclusion and exclusion criteria; and drug accountability records. The site provided the field investigator with electronic CRFs, contained on 4 CD disks. The field investigator compared the consistency between subjects' source data, CRFs, and data listings provided by the sponsor, with respect to primary and secondary endpoints, adverse events, concomitant medications and protocol deviations.

According to the field investigator, source documents reviewed consisted of study visit worksheet forms (titled NB-302 Source Documents), Concomitant Medications and Adverse Event Logs, lab reports electrocardiograms, progress notes, and subject questionnaire forms. The subject questionnaire forms were designed to gather information used to evaluate a subject's mood (insomnia, anxiety, depression, suicidal, stimulation), food cravings, and quality of life. The questionnaire forms were used in conjunction with the behavioral modification program assessment visits, and thus the subject was required to complete the form and sign at each visit. The questionnaire data was used in the evaluation of secondary efficacy and safety endpoints for this study.

b. General observations/commentary: The field investigator verified source data with electronic CRF data (on 4 CD disks provided at site), and the data listings (provided by sponsor), and no inconsistencies were found.

A one item FDA-483 was issued to Dr. Hill at the conclusion of the inspection. The item on the FDA-483 included: Failure to conduct investigation according to investigational plan. Specifically, the field investigator reported that the site did not ensure that lists of subjects' concomitant medications were reviewed by the sub-investigator/physician investigator, as was required by the protocol. According to the Study Delegation Log, Dr. Hill delegated the review of concomitant medications to 2 physician sub-investigators. The

field investigator noted that during a subject's study visit, the site study coordinator would document the name of the concomitant medication on a Concomitant Medication form, but there was no documentation demonstrating that the Concomitant Medication forms were then reviewed by Dr. Hill, or the two designated physician sub-investigators. This finding was observed across the board for all 30 subject records reviewed.

DSI Reviewer Comment: It appears that this occurred because the Concomitant Medication form did not contain a column for the investigator or sub-investigator to document his/her review. Of note, the listed concomitant medications were appropriately reported in the CRF, and included in the NDA data listings; therefore, the analyses provided by the Applicant in the NDA are not impacted.

In addition to the one item listed on the FDA-483, four items were discussed with Dr. Hill at the conclusion of the inspection: 1) the need for better documentation with regard to subject case records, including providing more complete documentation in the progress notes, that appeared on the Source Document Adverse Event or Concomitant Medication form, 2) the appearance of seemingly different handwritings, with respect to subjects signing and dating their questionnaire forms (see discussion in the next paragraph), 3) the need for the study coordinator (b) (6), also known as (b) (6) to sign the informed consent document with a full name versus first initial and last name, and 4) better reporting of protocol deviations to IRB and how decisions were made regarding "patient safety" (see discussion below).

DSI Reviewer's Note: With respect to the finding of different handwritings on subject questionnaire forms, the field investigator noted that subjects were required to date and initial each of the questionnaire forms, required for each visit. The field investigator noted that in some cases, the handwritings appeared distinct and different. As described in an earlier section, these questionnaire forms were designed to gather information used to evaluate a subject's mood (insomnia, anxiety, depression, suicidal ideation), food cravings, and quality of life, and the data was used for secondary analyses. Site staff were queried about apparent differences in handwriting, and both the Director, and Assistant Director, of (b) (6) (b) (6) stated that the subject always signed and dated their own forms. In addition, during the close-out visit, Dr. Hill reiterated that "at no time did the study staff complete anything that the subject was to complete." Additionally (b) (6) stated that there were occasions when the subject did not date and initial these forms, and in those cases, the fields were left blank. The field investigator asked (b) (6) if she could provide an example. (b) (6) left the room, and returned with an example of a form where the subject had not signed or dated it, and these fields were, in fact, blank.

In reviewing several sets of questionnaire forms that will be provided as exhibits in the Establishment Inspection Report (EIR), the DSI Reviewer notes it is not possible to determine if the handwritings are distinctly different for a given subject. Therefore, DSI has determined that there is no evidence of falsification of present.

With respect to the reporting of protocol deviations, the field investigator noted, that although there were numerous protocol deviations, only 3 had been reported (by the site) to the IRB. All

deviations, however, had been reported to the sponsor. When site staff was queried as to why all deviations were not reported to the IRB, they explained that the IRB directed that they only be notified of violations that affected patient safety. Given that protocol deviations appear to have been appropriately reported to the sponsor, this observation does not appear to impact the reliability of data submitted in the NDA.

c. Assessment of data integrity: Although a one observation Form FDA 483 was issued to this site and additional minor observations were discussed with Dr. Hill and his staff, the nature of the issues identified to not appear to significantly impact the reliability of data reported from this site in the NDA. Therefore, DSI recommends that study data from this site be considered reliable and acceptable in support of the requested indication.

NOTE: Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

4. Douglas Young, M.D.

Northern California Research
3840 Watt Ave., Bldg E
Sacramento, CA 95821

a. What was inspected: Dr. Young conducted Study NB-303: “A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained- Release (SR) and Placebo in Obese Subjects.” At this site, 91 subjects were screened, 73 subjects were enrolled, and 30 subjects completed the study. The field investigator compared the primary efficacy endpoint data listings to the source CRF for 30 subjects. In addition, the field investigator verified and reviewed secondary endpoints for > 10% body weight loss, change in fasting HDLs, change in triglycerides, change in LDLs, change in blood pressure and the Quality of Life form values in 24 study subjects. The inspection reviewed all adverse events to ensure they were accurately documented and reported.

The field investigator also reviewed 9 subject files for compliance with study visit procedures and assessments, including physical exams, waistline measurements, concurrent medications, clinical labs and questionnaire form documentation and completion. Study related correspondence, IRM approvals, informed consent documents, drug accountability logs, and monitoring logs were also reviewed during the inspection.

b. General observations: Primary efficacy endpoint data listings were compared to the source documents and electronic CRFs; the field investigator verified 100% concordance for the 30 subjects’ records reviewed. The field investigator verified as accurate, secondary endpoints for > 10% body weight loss, change in fasting HDLs, change in triglycerides, change in LDLs, change in blood pressure and the Quality of Life questionnaire form values in 24 study subjects’ records. The field investigator reported that adverse events were appropriately reported and followed with the exception of changes in blood pressure and heart rate/pulse rates

(observation #1 on the Form FDA 483). The field investigator also performed a reconciliation of drug inventory and reported that all study drug was accurately accounted for.

At the conclusion of the inspection, a three observation Form FDA 483 was issued to Dr. Young. Dr. Young responded to the Form FDA 483 in a letter dated July 30, 2010. The following observations were included on the Form FDA 483:

(1) Blood pressure or heart rate values that per the protocol should have been classified as adverse events were not reported or followed up. According to the protocol, an increase from baseline that are > 10 BPM for pulse rate, increase in diastolic blood pressure > 10 mm Hg, or increase in systolic blood pressure > 15 mm Hg should have been listed as adverse events. Heart rate or blood pressure elevations for Subjects 008, 009, 051, and 088 were not addressed, as per the protocol requirements.

DSI Reviewer's Note: In his response to the 483 observations, Dr Young stated he did not consider these increases in BP and/or pulse rate to be clinically significant, and therefore, had discretion in allowing the subject not to return in 72 hours for re-evaluation as required by the protocol. DSI considers this response acceptable.

(2) Informed consent in accordance with 21 CFR Part 50, was not obtained from each subject prior to drug administration and conducting study-related tests. Specifically, Subject #008-017 transferred from another study site and was not re-consented at Dr. Young's site on December 2, 2008 prior to undergoing study procedures. In addition, Subject #051 was not re-consented with the latest version of the ICD.

DSI Reviewer's Note: In his response letter, Dr. Young stated that the revised version of the ICD, approved on October 8, 2008 stipulated that the revised consent version is for new enrollees only. Since Subject #51 was not a new subject, this stipulation did not apply. With respect to Subject #008-017, who transferred from another site, Dr. Young stated that study procedures were conducted with only the subject's original ICD in place, and that he has amended his procedures so that all subjects who transfer from another site will be re-consented. DSI considers this response acceptable..

(3) Accurate records were not maintained with respect to informed consent documents. Specifically, page 21 of the ICD was missing during the consenting process for at least eight subjects (Subjects 039, 049, 050, 055, 061, 082, 086, and 091); therefore, Page 21 was not signed by the subjects.

DSI Reviewer's Note: Page 21 was the third and final page of a HIPAA document, which was a subset of the ICD. Since FDA does not have regulatory authority over HIPAA, this observation is not valid.

The FDA investigator also noted an inconsistency with respect to documentation in

the EIR. Specifically, progress notes documented that “Subject #063 was a screen failure, whereas the FDA investigator noted that it was in fact Subject #061, who was a screen failure (not Subject #063, as per documentation).

Additionally, the field investigator discussed several items with Dr. Young at the conclusion of the inspection. These items were considered isolated in nature, and at the FDA investigator’s discretion they were not included as observations on the Form FDA 483.

- a) Subject 008 received study drug medication of Subject 009 at one visit. However, the field investigator also noted that both subjects were on the same medication;
- b) Presence of a few write-overs and incorrect dates on study documents; however, the majority of corrections were done correctly. For example, Dr. Young signed a document dated June 22, 2010, even though he had been out of the country at this time. It appears that Dr. Young had signed and dated the document on his return, and used the date the document had been created for his signature.

DSI Reviewer’s Note: The EIR did not indicate how Dr. Young responded to this finding; however, as this appears to be an isolated example to backdating, DSI does not believe it raises concerns with overall data integrity at the site.

- c) The protocol required that the ECG called for Bazett’s conversion factor, whereas the inspection found that on some occasions an ECG with Hodge’s conversion factor was used.

DSI Reviewer’s Note: This finding was discussed with Dr. Eileen Craig, Medical Officer for this Application, who advised that this protocol deviation is unlikely to result in significant safety or efficacy concerns.

c. Assessment of data integrity: Although regulatory violations were noted at this site, they are unlikely to significantly impact primary efficacy or safety analyses; therefore, DSI recommends that the study data from this site be considered acceptable in support of the requested indication.

5. Philip Snell, M.D.

Mountain View Clinical Research, Inc.
406 Memorial Drive Extension
Greer, SC 29651

a. What was inspected: Dr. Snell conducted 2 studies at his site:

Study NB-303: “A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained- Release (SR) and Placebo in Obese Subjects”;

Study NB-304: “A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone 32 mg Sustained Release (SR)/Bupropion 360 mg Sustained Release (SR) and Placebo in Obese Subjects with Type 2 Diabetes Mellitus.

Audits of both studies were conducted during the FDA inspection.

For Study NB-303, at this site 59 subjects were screened, 41 subjects were enrolled, 18 subjects were screen failures, and 16 subjects completed the study. Twenty-five subjects withdrew consent or were lost to follow-up. The field investigator conducted a thorough review of 8 (of 59) subject files, including verifying that all endpoint data was correctly reported; protocol deviations, such as out-of-window visits, and exclusionary medications, were properly addressed with the sponsor; and that inclusion and exclusion criteria were met. The field investigator ensured consistency between source data, CRF documentation/data, and NDA data listings for the following subjects: 003, 007, 012, 014, 021, 025, and 040.

For Study NB304, at this site 48 subjects were screened, 20 subjects enrolled, 28 subjects were screen failures, and 9 subjects completed the study. Eleven subjects withdrew consent or were lost to follow-up. The field investigator reviewed 9 (of 48) subject files, including: review of source data and CRFs; that inclusion and exclusion criteria were met; that protocol deviations were properly reported; and that adverse events, including SAEs were accurately reported and documented. No discrepancies were noted.

b. General Observations:

Study NB-303:

Study files were well-organized and well-maintained, and there were no major discrepancies between source data, CRF data and data listings. All protocol deviations were properly addressed and reported; the majority of protocol deviations pertained to the use of excluded medications, and late study visits. Adverse events were properly reported; no SAEs were experienced by any of the subjects reviewed. Drug accountability records were accurately maintained.

Study NB-304:

Source documents were reported as well-organized. The study required several secondary efficacy measurements that were obtained through responses to subject questionnaires, such as the Food Craving Inventory, the Control of Eating Questionnaire, and the Impact of Weigh on the Quality of Life Questionnaire. The field investigator reported no discrepancies between the source and data listings for the files audited. In addition, the field investigator compared electronic case report forms to the data listings and found no discrepancies.

Adverse events and concomitant medications were properly documented. One SAE for subject 003, was not reported to the IRB in a timely manner (Subject 003 reportedly had kidney stones and was hospitalized on August 26, 2007, and discharged on August 28,

2007. The subject was subsequently discontinued from the study due to opioid usage prescribed for pain management). The event was reported to the sponsor on August 31, 2007; however, no initial report was sent to the IRB. A follow-up report was submitted to the IRB on March 25, 2008. This was explained by site staff as an oversight.

Protocol deviations were reviewed. The majority of deviations pertained to visits outside of window, drug titration instructions not followed, and incomplete or questionable answers on questionnaires. All appeared on the NDA data listings.

Drug accountability records, IRB and sponsor correspondence, monitoring logs, financial disclosures, Form FDA 1572s, protocol deviation memos, and laboratory certificates appeared in order.

c. Assessment of data integrity: Based on review of the inspectional findings for Dr. Snell's site, the study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the respective indication.

6. Orexigen Therapeutics, Inc.

3344 N. Torrey Pines Court,
La Jolla, CA 92037

a. What was inspected: The inspection covered the firm's management of the four protocols (NB-301, NB-302, NB-303, & NB-304) submitted under NDA 200-063. The field investigator reported that all study related sponsor responsibilities for the conduct of the studies had been transferred to contract vendors, and notified DSI of this fact during the inspection on August 31, 2010. At that time, DSI advised the field investigator to continue the inspection, and to focus on the sponsor's oversight of the contracted vendors.

b. General Observations: The field investigator reported that the firm (Orexigen) had no previously approved products. During the inspection a list of all vendors/responsible individuals used by the firm for each protocol was obtained. These were reported as follows:

- i) (b) (4) – study conduct and monitoring
- ii) (b) (4) – data and statistical management
- iii) (b) (4) – electronic case report forms (eCRF)
- iv) (b) (4) – project management, consulting services, regulatory, CMC
- v) (b) (4) – Packaging and labeling, study drug supplies, study drug distribution, drug returns, (b) (4) (central randomization)
- vi) (b) (4) – manufacturer of study drug.

The field investigator noted that appropriate vendor contracts were in place for the various CROs prior to commencement of the studies. The field investigator also noted that the sponsor had notified and submitted documents to CDER regarding the transfer of regulatory responsibilities. A list of all study monitors used for the studies by (b) (4) was obtained; based on a randomly selected sample, the field investigator noted that monitors' qualifications were adequate. The field investigator reviewed monitoring reports for the top-enrolling investigator for each protocol, and reported that monitoring was conducted according to and in compliance with pre-specified monitoring plans.

The field investigator asked if the sponsor terminated any investigators from the study. The sponsor stated that one site (site 100 – Dr. Sewart) was investigated for fraud. Dr. Dunayevich, Chief Medical Officer Orexigen, was actively involved in the review of the findings, and Orexigen indicated that because of the findings, they had stopped all screening at the site. Copies of the site's monitoring reports, the audit report, and the site's corrective action plan were collected by the field investigator. According to the FDA field investigator, it appeared that a study coordinator at the site knowingly permitted a nurse to use a fictitious name to enroll in the study without the knowledge of the Dr. Stewart. This issue was identified by study monitors and the issue was appropriately escalated. As a result the Sponsor did not reopen enrollment at the site, but did allow subjects already enrolled to complete the study.

The field investigator asked for the SAEs and AEs for the studies. Orexigen printed out the data listings sent to FDA. The field investigator reviewed a subset of the AE listings and did not note anything that should have been reported as an SAE.

The field investigator noted that clinical trial data was reported by electronic-CRFs, which were completed by site personnel administering the study procedures and signed off by the principal investigator at each site. The field investigator reported that the sponsor contracted out the development and maintenance of the e-CRF database to (b) (4). During the inspection, the validation summary for the e-CRF databases was reviewed and was found to be 21 CFR Part 11 compliant for all studies.

At the conclusion of the Orexigen inspection, no Form FDA 483 was issued. However, several items were discussed with the Sponsor:

1. A recommendation that telephone logs be maintained to document discussions between the CRO's medical monitor and the sponsor's chief medical officer, regarding SAEs and all other study-related issues. The field investigator advised that all e-mails between the two parties should be placed into separate binders; and that minutes should be recorded for all meetings held.
2. A recommendation that monitoring reports be more closely scrutinized by area, such as drug accountability. For example, at Dr. Hill's site, drug accountability was pushed back for 6 consecutive visits. At the close of the inspection, though ultimately resolved, this site had drug accountability problems that could have been handled earlier had site monitoring records been reviewed in a more timely manner.

c. Assessment of data integrity: The majority of responsibilities for the conduct of the studies for this NDA were transferred to contract vendors. Based on review of study related records held by Orexigen, it appears that their oversight of studies NB 301, NB 302, NB 303, and NB 304 was adequate, and that data reported in the NDA may be considered reliable.

Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For this NDA, 5 clinical site inspections and 1 sponsor inspection were conducted. The sites selected for inspection were, for the most part, high enrollers for their respective study. The sponsor inspection was performed to evaluate the sponsor's oversight of the study, and because this was a new molecular entity.

Final classifications of inspections at Dr. Grave's (protocol NB 301), Dr. Griffin's (protocol NB 301), and Dr. Snell's (protocols NB 303 and NB 304) sites are NAI and DSI recommends that the data from these sites be considered reliable in support of the respective indications.

With respect to the inspection of Dr. Hill's site (protocol NB 303) and Dr. Young's site (protocol NB 302), while regulatory violations were identified (primarily related to documentation and recordkeeping), overall reliability of the data generated by these sites appears sufficient to recommend that the data be used in support of the NDA.

With respect to the Sponsor inspection, oversight of vendors relating to Studies NB 301, NB 302, NB 303, and NB 304 was adequate, and data reported in the NDA may be considered reliable.

NOTE: The EIR (Establishment Inspection Reports) from inspections at the clinical site #28 (Hill) and the sponsor site (Orexigen) have not yet been received or reviewed by DSI. Observations noted above are based on the Form FDA 483 and/or communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

/s/

SHARON K GERSHON
12/06/2010

JEAN M MULINDE
12/06/2010
Reviewed and signed for Tejahsri Purohit-Sheth, M.D.



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: October 1, 2010

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Meghna Jairat
Regulatory Project Manager
Division of Metabolic and Endocrine Products

Subject: QT-IRT Consult to NDA 200063

This memo responds to your consult to us dated June 21 2010 regarding QT analysis report, sponsored by Orexigen Therapeutics Inc. The QT-IRT received and reviewed the following materials:

- Your consult
- NDA 200063 (SDN001)
- Study NB-228
- Study NB-303

QT-IRT Comments for DMEP

Large changes in QTc intervals were not observed in studies NB-228 and NB-303. However, the trial design is not sufficient to rule out small changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms), as defined by ICH E14 guidance. If the Division intends to approve the product, a thorough QT study should be considered as part of the PMR. QT-IRT would like to review the study protocol prior to conducting the study. In addition, QT-IRT suggests no labeling language to be included in section 12.2. Further language can be added once the thorough QT study results are available.

In addition, we recommend the sponsor submit outlier analysis results for PR and QRS intervals in diabetic patients. QT-IRT would like to review the relevant material

BACKGROUND

The sponsor did a QT analysis using data from a Phase 1 (NB-228) and Phase 3 (NB-303) trials as proposed in their plan during the EOP 2 meeting. The review division is asking for our review and comments on this analysis.

CONTRAVE[®] (naltrexone HCl and bupropion HCl) Extended-Release Tablets is intended for the treatment of obesity and weight management. In the correspondence in October 2009, the sponsor raised a question on whether the QT analyses using data from Phase 1 (NB-228) and Phase 3 (NB-303) trials as proposed in the EOP2 meeting were sufficient to support the evaluation of the CONTRAVE-effects on QTc interval. The Division indicated that to determine whether a thorough QT study is warranted should be based on the review of the data submitted. In 31 March 2010, the sponsor submitted the QT analyses results as part of the NDA submission.

(b) (4)

The active pharmaceutical ingredients in CONTRAVE drug product are naltrexone HCl, a potent μ (mu) opioid antagonist, and bupropion HCl, a biogenic amine reuptake inhibitor, mainly of dopamine (DA) and norepinephrine (NE). CONTRAVE drug product is provided as tablets containing either 4 mg or 8 mg of naltrexone HCl and 90 mg of bupropion HCl (4 mg/90 mg tablet and 8 mg/90 mg tablet).

The clinical development program enrolled a total of 3,473 subjects exposed to CONTRAVE in Phase 2 and 3 studies for a total of 2,313 subject years. The recommended maintenance doses are naltrexone 16 and 32 mg/day in combination with bupropion 360 mg/day (NB16 and NB32, respectively).

Table 1. CONTRAVE Dosing Regimen During the Maintenance Period

NB Tablet Strength	Dosing Regimen	Total Daily Dose
4 mg naltrexone SR / 90 mg bupropion SR	2 tablets twice daily (BID)	16 mg naltrexone SR / 360 mg bupropion SR
8 mg naltrexone SR / 90 mg bupropion SR	2 tablets twice daily (BID)	32 mg naltrexone SR / 360 mg bupropion SR

Source: Risk Management Plan, Table 2-1

Although CONTRAVE has not yet been marketed, the individual active components (naltrexone and bupropion) have been approved for other indications and widely used over the past 20 years.

-Previous Marketing Experience:

Bupropion hydrochloride was first marketed as an immediate-release (IR) tablet formulation in the US in 1985. Three formulations of bupropion are currently available in the US: an IR tablet (Wellbutrin[®]), a sustained-release tablet (Wellbutrin SR[®]), and an extended-release tablet (Wellbutrin XL[®]), each used for the treatment of depression and seasonal affective disorder. Bupropion is also available under the trade name Zyban[®] SR as an aid to smoking cessation treatment. In the US, generic formulations of bupropion are also available. Naltrexone has been marketed in the US since 1984. Naltrexone IR is currently approved for the treatment of opioid addiction (1984) and alcohol dependence (1995) (ReVia[®], formerly Trexan[®], and Depade[®]). More recently (2006), an extended-release injectable suspension formulation of naltrexone

(Vivitrol®) was approved by the Food and Drug Administration (FDA) for the treatment of alcohol dependence.

Reviewer's Comments: The proposed therapeutic doses of bupropion and naltrexone in the CONTRAVE extended release formulation are lower than those previously approved for other indications.

-Non-Clinical Experience:

The objective of this study was to assess the effects of Naltrexone and its major metabolite (6-Beta Naltrexol) on the rapidly activating inward rectifying potassium current (IKr) conducted by hERG (human ether-a-go-go related gene) channels stably expressed in a HEK293 cell line. The effects of Naltrexone and 6-Beta Naltrexol on the hERG related potassium current was assessed using whole-cell patch clamp electrophysiology methods. The effects of Naltrexone and 6-Beta Naltrexol will be quantified using a concentration-response relationship and, if appropriate, generation of an IC₅₀ concentration.

(b) (4)
Study Number 1560-001
Evaluation of the Effects of Naltrexone and 6-Beta Naltrexone on Cloned hERG Channels Expressed in Human Embryonic Kidney (HEK293) Cells

Concentration	Summary of hERG Current Inhibition, %		
	Inhibition, % Mean	SEM	N
0 µM (PSS with 0.1% DMSO)	0.51	0.273	3
0.02 µM Naltrexone	0.62	0.253	3
0.1 µM Naltrexone	0.96	0.703	3
0.3 µM Naltrexone	-1.11	0.947	3
3 µM Naltrexone	6.02	1.669	3
0.3 µM 6-Beta Naltrexol	0.20	0.704	3
1 µM 6-Beta Naltrexol	-0.31	0.109	3
3 µM 6-Beta Naltrexol	0.06	0.185	3
10 µM 6-Beta Naltrexol	5.78	1.054	4
0.1 µM Cisapride	77.95	1.537	3

Reviewer's comments: hERG assays for Naltrexone and Naltrexol are reported and neither Naltrexone nor Naltrexol inhibit hERG currents within the therapeutic exposure range. No hERG assay for bupropion was provided. Moreover, a literature search did not provide information concerning the effect of bupropion on hERG currents.

-Clinical Experience:

From Summary of Clinical Safety (2.7.4) and Integrated Summary of Safety

The safety and tolerability of NB was evaluated in 23 studies, including 15 Phase 1, four Phase 2, and four Phase 3 investigations. The vast majority of exposures to NB are from the Phase 3 studies and NB-201; a total of 3473 subjects have been exposed to NB in Phase 2 and 3 studies for a total of 2313 subject years.

The ISS and Summary of Safety (2.7.4) were primarily based on pooled data from the Phase 2 and Phase 3 studies. The ISS includes three datasets: the primary placebo-controlled integrated safety analysis dataset, the overall NB exposure integrated safety analysis dataset and the secondary placebo-controlled integrated safety analysis dataset of subjects without type 2 diabetes (hereafter referred to as the Primary, Overall, and Nondiabetic datasets).

Electrocardiogram results (ISS, page 321)

Clinically significant ECG abnormalities were to be recorded as AEs and are discussed in M5.3.5.3, ISS Section 2.1.5.2. Quantitative analyses of ECG intervals including ventricular rate, PR, QRS, and corrected QT are discussed in this section. It should be noted that the PR interval was recorded as 0 (zero) for ECGs from subjects with atrial fibrillation. As suggested in the E14 guidance for Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (October, 2005), QT measurements are corrected for heart rate at the time according to Bazett's (QTcB) and Fridericia's (QTcF) equations and results were reported in Table ISS.P.9-1. QT corrections according to Bazett's equation, derived from the ECG machine, are reported in Table ISS.P.9-1.

ECGs: Primary datasets. Small mean changes from baseline to endpoint were recorded in each treatment group (ISS Table 4-56); overall, there were no clinically relevant differences between the Total NB and the placebo groups and no evidence of either an NB or dose effect for any parameter.

Categorical analyses of QTcF intervals showed that no subjects had a QTcF interval >500 ms and <1% of subjects had a QTcF increasing ≥ 60 ms from baseline (0.6% Total NB vs. 0.4% placebo). A QRS interval >110 ms was infrequent in both the Total NB and placebo groups (2.8% and 1.9%, respectively). The incidence of a low PR interval (<120 ms) or a high PR interval (>200 ms and increase >20 ms from baseline) was low and similar between the Total NB (2.0% and 1.1%, respectively) and placebo (2.6% and 1.3%, respectively) groups. These data are summarized in Table 4-58; complete data are provided in Table ISS.P.9-5.

Treatment-emergent ECG results are consistent with a lack of study drug effect on ECG parameters, including corrected QT. These data are summarized in Table 4-58; complete data are provided in Table ISS.P.9-5.

Table 2. Treatment-Emergent Electrocardiogram Results in Subjects with Normal Baseline Measurements: Primary Dataset, Double-Blind Treatment Phase

	Placebo		NB16		NB32		Total NB	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
QTcF								
>450 msec ^a	1364	48 (3.5%)	515	14 (2.7%)	2155	57 (2.6%)	2701	72 (2.7%)
>480 msec ^b	1393	2 (0.1%)	527	1 (0.2%)	2212	3 (0.1%)	2770	4 (0.1%)
>500 msec (PCS High) ^c	1393	0	527	0	2213	0	2772	0
≥30 msec from BL ^a	1364	82 (6.0%)	515	30 (5.8%)	2155	116 (5.4%)	2701	147 (5.4%)
≥60 msec from BL ^a	1364	5 (0.4%)	515	4 (0.8%)	2155	11 (0.5%)	2701	15 (0.6%)
PR Interval								
<120 msec (PCS Low)	1361	35 (2.6%)	515	10 (1.9%)	2180	45 (2.1%)	2728	55 (2.0%)
>200 msec & increase >20 msec from BL (PCS High)	1348	17 (1.3%)	517	3 (0.6%)	2144	27 (1.3%)	2694	30 (1.1%)
QRS Interval								
>110 msec (PCS High)	1359	26 (1.9%)	516	12 (2.3%)	2147	63 (2.9%)	2695	75 (2.8%)

Data Source: Table ISS.P.9-5.

^a Subjects with a value >450 msec at baseline were excluded.

^b Subjects with a value >480 msec at baseline were excluded.

^c Subjects with a value >500 msec at baseline were excluded.

Abbreviations: BL=baseline; PCS=potentially clinically significant; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Source: ISS, Table 4-58.

Overall datasets had the same trend as the primary datasets shown above.

Reviewer's comments:

- No differences in incidence in QTcF and PR duration and in changes over baseline were seen between treatment arms in the primary dataset.
- The incidence in QRS > 110 ms in the NB16 and NB 32 arm is slightly higher than in the placebo arm.

ECG Comparison of Diabetic and Nondiabetic Datasets (ISS, page 336)

Mean change in ventricular rate, PR and QRS intervals, and QTcF values at baseline and endpoint in the Diabetic Dataset in both the NB32 and placebo groups were generally greater than those in the Nondiabetic Dataset. Subjects in the Diabetic Dataset receiving NB32 showed small (less than 3 ms) increases in QTcF and QT mean change values at endpoint compared with Subjects in the Nondiabetic Dataset receiving NB32 who showed decreases in QTcF and QT mean change values at endpoint (Table 4-64; source: Table ISS.S.9-1 and Table 14.3-44 in Study NB 304 CSR).

Table 3. Electrocardiogram Parameters at Baseline and Endpoint: Diabetic and Nondiabetic Datasets, Double-Blind Treatment Phase

	Nondiabetic Dataset				Diabetic Dataset			
	Placebo (N=1346)		NB32 (N=2212)		Placebo (N=169)		NB32 (N=333)	
	BL	Endpt	BL	Endpt	BL	Endpt	BL	Endpt
Ventricular Rate (bpm)								
Mean	68.16	66.67	68.42	68.65	70.92	70.84	71.89	72.24
Mean change from BL	--	-1.49	--	0.23	--	-0.08	--	0.35
Minimum	44.00	43.00	42.00	40.00	50.00	46.00	49.00	43.00
Maximum	100.00	108.00	106.00	105.00	105.00	104.00	105.00	118.00
PR (msec)								
Mean	158.60	159.52	158.78	159.03	164.57	166.60	164.63	165.03
Mean change from BL	--	0.93	--	0.25	--	2.03	--	0.40
Minimum	96.00	0.00	98.00	76.00	0.00	0.00	104.00	0.00
Maximum	256.00	400.00	262.00	244.00	322.00	360.00	300.00	326.00
QRS Duration (msec)								
Mean	87.86	87.88	88.64	89.34	89.57	89.80	93.25	93.09
Mean change from BL	--	0.02	--	0.70	--	0.23	--	-0.16
Minimum	35.00	40.00	27.00	27.00	40.00	21.00	8.00	30.00
Maximum	164.00	160.00	168.00	168.00	166.00	168.00	168.00	162.00
QT (msec)								
Mean	396.20	399.52	396.41	393.44	389.55	391.71	385.75	388.39
Mean change from BL	--	3.32	--	-2.97	--	2.16	--	2.64
Minimum	300.00	280.00	280.00	246.00	320.00	312.00	180.00	280.00
Maximum	512.00	504.00	524.00	512.00	474.00	496.00	471.00	468.00
QTcF (msec)								
Mean	409.84	410.53	410.57	408.16	408.16	409.12	405.68	408.36
Mean change from BL	--	0.70	--	-2.41	--	0.96	--	2.69
Minimum	319.48	299.46	305.80	289.00	320.00	326.57	297.48	299.46
Maximum	477.74	474.04	491.06	492.67	474.00	488.35	460.84	491.17

Data Source: Table ISS.S.9-1 and Table 14.3-44 in Study NB-304 CSR.
Abbreviations: BL=baseline, Endpt= endpoint.

Source: ISS, Table 4-64, page 336.

Categorical analysis of ECG measurements at baseline showed that no subjects had a treatment-emergent QTcF value >500 ms in either the Diabetic or Nondiabetic Dataset. The incidence of treatment-emergent changes in ECG results were higher for the Diabetic Dataset compared with the Nondiabetic Dataset in both the Total NB and placebo groups for all other prespecified criteria (Table 4-65). Greater incidences of QTcF values >450 ms were observed in the Diabetic Dataset in both the NB32 and placebo groups (3.0% and 4.1%, respectively) compared with the Nondiabetic Dataset (2.6% and 3.4%, respectively). Greater incidences of QTcF values ≥ 30 msec from baseline were observed in the Diabetic Dataset in both the NB32 and placebo groups (9.3% and 7.7%, respectively) compared with the Nondiabetic Dataset (4.5% and 5.7%, respectively). Greater incidences of QTcF values ≥ 60 ms from baseline were also observed in the Diabetic Dataset in both the NB32 and placebo groups (1.5% and 1.2%, respectively) compared with the Nondiabetic Dataset (0.4% and 0.2%, respectively).

Table 4. Treatment-Emergent Electrocardiogram Results: Diabetic and Nondiabetic Datasets, Double-Blind Treatment Phase

ECG Parameter	Nondiabetic Dataset				Diabetic Dataset	
	Placebo (N=1346)		NB32 (N=2212)		Placebo (N=169)	NB32 (N=333)
	N	n (%)	N	n (%)	n (%)	n (%)
QTcF						
>450 msec ^a	1207	41 (3.4%)	1874	48 (2.6%)	7 (4.1%)	10 (3.0%)
>480 msec ^b	1232	0	1922	1 (<0.1%)	NA	NA
>500 msec (PCS) ^c	1232	0	1923	0	0	0
≥30 msec from BL	1232	70 (5.7%)	1923	86 (4.5%)	13 (7.7%)	31 (9.3%)
≥60 msec from BL	1232	3 (0.2%)	1923	7 (0.4%)	2 (1.2%)	5 (1.5%)
PR Interval						
<120 msec (PCS low)	1205	31 (2.6%)	1895	39 (2.1%)	NA	NA
>200 msec & >20 msec from BL (PCS high)	1200	11 (0.9%)	1868	22 (1.2%)	NA	NA
QRS Interval						
>110 msec (PCS high)	1206	17 (1.4%)	1882	45 (2.4%)	NA	NA

Data Source: Tables ISS.S.9-5 and ISS.S.9-6, and Table 14.3-43 in Study NB-304 CSR.

^a Subjects with a value >450 msec at baseline were excluded.

^b Subjects with a value >480 msec at baseline were excluded.

^c Subjects with a value >500 msec (nondiabetic subjects) or ≥500 msec (subjects with diabetes) were excluded.

Note: Data for the ≥30 msec and ≥60 msec from baseline were included from Table ISS.S.9-6 for the Nondiabetic Dataset to match the data analyzed for the Diabetic Dataset (both include subjects with a baseline QTcF value >450 msec).

Abbreviations: BL=baseline; NA=not available; PCS=potentially clinically significant.

Source: ISS, Table 4-65, page 337.

Reviewer's comments:

- A higher incidence of subjects with QTcF ≥30 ms and ≥60 ms was seen in the Diabetic Dataset compared to the Non Diabetic Dataset in both, the NB32 (naltrexone SR 32mg / Bupropion SR 360 mg) and placebo groups.
- Within the Diabetic Dataset the incidence in QTcF ≥30 ms was slightly higher in the NB32 arm compared to the placebo arm.
- In the Non Diabetic Dataset no differences in incidence in PR outliers between placebo and NB 32 arm was seen.. In the Diabetic Dataset, the PR outlier analysis was not available.
- In the Non Diabetic Dataset, the incidence of subjects with a QRS > 110ms was slightly higher in the NB32 arm compared to the placebo arm. No QRS outlier analysis was submitted in the Diabetic Dataset.

Adverse Events

From Summary of Clinical Safety, eCTD 2.7.4.2.1

-All AEs -Primary dataset

Notable TEAEs (i.e., TEAEs occurring at a ≥5% incidence in the Total NB group and at least twice the incidence of the placebo group; see Section 2.7.4.2.1) occurring during the double-blind treatment phase were nausea, constipation, vomiting, dizziness, and dry mouth. During the titration phase, headache and insomnia also met these criteria. TEAEs other than those related to upper respiratory tract infection were generally reported at a lower incidence in the 52-week maintenance phase compared with the titration phase; nausea and vomiting were the only TEAEs that met the defined criteria during the maintenance phase.

Other TEAEs of interest (defined as those TEAEs that occurred at a $\geq 2\%$ incidence in the Total NB group and at least twice the incidence of placebo) occurring during the double-blind treatment phase were tremor, hot flush, tinnitus, abdominal pain upper, dysgeusia, hyperhidrosis, and palpitations (Table 2.7.4-14). During the titration phase, anxiety was also noted as a TEAE of interest. No additional TEAEs of interest were reported during the maintenance phase. These events were rarely or never serious, rarely severe and infrequently resulted in treatment discontinuation, and they are consistent with the AE profiles for the individual components of NB (bupropion and naltrexone).

Table 5. Incidence (%) of Treatment-Emergent Adverse Events ($\geq 2\%$ Total NB and at Least Twice the Incidence of Placebo): Primary Dataset, Double-Blind Treatment Phase

Preferred Term	Placebo (N=1515)	NB16 (N=633)	NB32 (N=2545)	Total NB (N=3239)
Nausea	6.7	27.6	32.5	31.8
Constipation	7.2	15.0	19.2	18.1
Vomiting	2.9	6.5	10.7	9.9
Dizziness	3.4	8.2	9.9	9.6
Dry mouth	2.3	7.4	8.1	7.9
Tremor	0.7	3.6	4.0	3.9
Hot flush	1.2	2.5	4.2	3.8
Tinnitus	0.6	4.3	3.3	3.4
Abdominal pain upper	1.3	2.1	3.5	3.1
Dysgeusia	0.7	2.2	2.4	2.4
Hyperhidrosis	0.6	1.6	2.6	2.4
Palpitations	0.9	3.5	2.1	2.4

Data Source: Table ISS.P.6.1-3.1

TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date \leq AE onset date \leq last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]).

Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment including NB48; TEAE= treatment emergent adverse event.

Source: Table 2.7.4-14, Summary of Clinical Safety

-Cardiovascular AEs

Table 6. Incidence of Blood Pressure and Pulse-Related Treatment-Emergent Adverse Events: Primary Dataset, Double-Blind Treatment Phase

Subtopic	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Subjects with any TEAE	64 (4.2%)	29 (4.6%)	161 (6.3%)	192 (5.9%)
Hypertension	60 (4.0%)	22 (3.5%)	149 (5.9%)	173 (5.3%)
Hypotension	0	0	1 (<0.1%)	1 (<0.1%)
Bradycardia	1 (<0.1%)	3 (0.5%)	1 (<0.1%)	4 (0.1%)
Tachycardia	3 (0.2%)	4 (0.6%)	17 (0.7%)	21 (0.6%)
Subjects with any treatment-emergent SAE	0	0	0	0
Subjects discontinued due to AE	4 (0.3%)	7 (1.1%)	17 (0.7%)	25 (0.8%)
Hypertension	3 (0.2%)	6 (0.9%)	17 (0.7%)	24 (0.7%)
Hypotension	0	0	0	0
Bradycardia	1 (<0.1%)	0	0	0
Tachycardia	0	1 (0.2%)	0	1 (<0.1%)

Data Source: Table ISS.P.BP.1-1, Table ISS.P.BP.2-1, Table ISS.P.BP.3-1

TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]).

Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event;

Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Source: 2.7.4 Summary of Clinical Safety, Table 2.7.4-21

Table 7. Incidence of Cardiovascular Treatment-Emergent Adverse Events: Primary Dataset, Double-Blind Treatment Phase

Subtopic	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Subjects with any TEAE	115 (7.6%)	54 (8.5)	205 (8.1%)	262 (8.1%)
Atherosclerotic Disease	86 (5.7%)	42 (6.6%)	164 (6.4%)	208 (6.4%)
Arrhythmias	27 (1.8%)	12 (1.9%)	35 (1.4%)	47 (1.5%)
Congestive Heart Failure	13 (0.9%)	4 (0.6%)	19 (0.7%)	24 (0.7%)
Subjects with any treatment-emergent SAE	7 (0.5%)	1 (0.2%)	8 (0.3%)	9 (0.3%)
Atherosclerotic Disease	6 (0.4%)	1 (0.2%)	6 (0.2%)	7 (0.2%)
Arrhythmias	3 (0.2%)	0	0	0
Congestive Heart Failure	1 (<0.1%)	0	3 (0.1%)	3 (<0.1%)
Subjects discontinued due to AE	21 (1.4%)	8 (1.3%)	21 (0.8%)	30 (0.9%)
Atherosclerotic Disease	13 (0.9%)	6 (0.9%)	12 (0.5%)	19 (0.6%)
Arrhythmias	7 (0.5%)	1 (0.2%)	4 (0.2%)	5 (0.2%)
Congestive Heart Failure	1 (<0.1%)	1 (0.2%)	5 (0.2%)	6 (0.2%)

Data Source: Table ISS.P.CV.1-1, Table ISS.P.CV.2-1, Table ISS.P.CV.3-1

TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]).

Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event;

Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Source: 2.7.4 Summary of Clinical Safety, Table 2.7.4-22

-Deaths (From Summary of Clinical Safety, eCTD 2.7.4.2.1.1.3)

One death was reported in the overall dataset of 5022 subjects (3507 received NB and 1515 received placebo). Subject 099-NB-301-003, a 65-year-old White male in the NB32 group, with a relevant medical history of active gout, hypercholesterolaemia, hypertension, idiopathic bradycardia, arthralgia, and psoriasis, experienced myocardial infarction (verbatim: myocardial infarction) on Day 324. The event was fatal. Per the medical examiner narrative, the manner of death was ruled as natural and the cause of death was atherosclerotic coronary artery disease. The last dose of study drug was on Day 324. The event of myocardial infarction was classified as severe and serious and judged by the investigator to be unlikely related to study drug.

Reviewer's comment:

- *None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred.*
- *Hypertension was the most common blood pressure-linked TEAE.*

-Studies submitted by the sponsor

Study NB-228

Title: A Phase 1, Bioequivalence Study of Two Different Formulations of Naltrexone SR/Bupropion SR Combination Trilayer Tablets Under Fasting Conditions.

This was a Phase 1, single-center, open-label, randomized, single oral dose, 2-way crossover study to assess the bioequivalence of 2 different formulations of naltrexone SR/bupropion SR combination trilayer tablets under fasting conditions with a minimum 9-day washout between dosing days in healthy adult subjects. The study was conducted in a total of 40 healthy male and female subjects between the ages of 18 - 60 years, inclusive. Subjects received 2 different formulations of naltrexone SR/bupropion SR (8/90mg) combination trilayer tablets

A 12-lead ECG was performed at screening, at each treatment period at 4 hours post-dose, and the final study visit (Day 13 or early termination).

ECG measurements occurred at screening, at each treatment period at 4 hours post-dose, and discharge. These results are listed in by-subject data listings. Frequency counts of the results were presented for each time point by treatment. Screening values were defined as the last observation obtained prior to dosing (including rechecks). Rechecks were not included as final visit observations. ECG results were classified as normal and abnormal, and a shift table was created to describe shifts from screening to final visit. ECG information is listed by subject and time point of collection for the safety population. There were no clinically significant ECGs from screening through discharge. Clinically insignificant abnormalities in the ECG findings appeared to be isolated instances.

Study NB-303

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Obese Subjects

Male or female subjects, aged 18 to 65 years (inclusive), with uncomplicated obesity or obesity associated with controlled hypertension and/or dyslipidemia were eligible to participate. Subjects assigned to NB32 were randomized within each study center to two alternative titration schedules of naltrexone SR (fast vs. slow). Beginning on Week 28 through Week 44, NB32-treated subjects who failed to achieve or maintain at least 5% body weight loss from baseline were re-randomized (1:1 ratio) to continue NB32 or receive NB48 (i.e., naltrexone SR 48 mg, while the dose of bupropion SR was 360 mg for both groups). This study included screening, drug titration period (Weeks 1 to 4), and maintenance (Weeks 5 to 56) period.

A standard 12-lead ECG was performed by qualified study staff at screening (baseline value), and Weeks 4, 24, and 56 (or early termination) and was read by the investigators at the study centers. At Weeks 4 and 56 (or early termination), ECG recordings were performed immediately after the PK sample was collected (subset of study sites who collected PK samples, Section 9.5.1.2.6). The ECG parameters included ventricular rate, PR interval, QRS duration, QT interval, and corrected QT interval using Bazett's (QTcB) and Fridericia's (QTcF) correction methods. Any clinically significant ECG changes from baseline were recorded on the AE eCRF.

Electrocardiogram results were listed and summarized in terms of the number and percentage of subjects with abnormal and normal findings at each assessment, change from baseline, and if applicable, clinically significant changes at each assessment. Additionally, change from baseline to endpoint, change from baseline by visit, and change from baseline to maximum were summarized using descriptive statistics for QT interval values (corrected and uncorrected), ventricular rate, PR interval, and QRS duration. Changes from baseline were calculated using the baseline values defined as observed on the first day of study drug dosing or prior to the first dose of study drug if baseline values were unavailable. Subjects with missing data for a given timepoint did not contribute to the tabulations for that timepoint. If multiple ECG results existed for a post-baseline timepoint, then the one closest to the scheduled visit was used for that visit. If there are two equally closest to the scheduled visit, the last one was used for that visit. The measured QT intervals were corrected using QTcB and QTcF methods. Categorical analyses of QT/QTc interval data were provided for the number and percentage of subjects at baseline and endpoint (Week 56 or upon early termination)

Parametric analysis of change from baseline for QT or QTcB, or QTcF between NB treated subjects and placebo for the safety population was conducted. The analysis used an ANOVA model with treatment, pooled study center and baseline. Subjects were included in this analysis if their ECG assessment was performed within 4 hours of the PK sampling time. In addition, regression analysis of QT and QTc versus plasma concentration was performed for each analyte (naltrexone, bupropion and their metabolites).

Review of ECG evaluations indicated no noteworthy changes from baseline across the treatment groups and no difference between groups in changes in ECG intervals including QTc, occurrence of ECG-related serious or non-serious TEAEs, or individual clinically significant ECG findings.

Reviewer's comments:

Large changes in QTc intervals were not observed in studies NB-228 and NB-303. However, the trial design is not sufficient to rule out small changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms), as defined by ICH E14 guidance.

- *No positive control was included in Study NB-228 or Study NB-303 to demonstrate assay sensitivity.*
- *In both studies the number of ECGs collected was insufficient to capture the potential maximum QTc prolongation.*
- *In Study NB 303, PK samples were collected incorrectly. For some subjects, there is no time-matched PK sampling. For other subjects, PK was collected immediately prior to ECG assessment.*
- *It is unclear whether adequate number of subjects was included in the trial to rule out small changes in QTc interval, as defined by ICH E 14 guidance.*

-Reviewer's MGPS Data Mining Analysis

We conducted an MGPS data mining analysis of the AERS database to study the disproportional reporting of adverse event codes with bupropion and naltrexone. To perform this analysis we selected reports containing Preferred Terms (PTs) associated with changes in ECG intervals duration that involved any PR, QRS and QT event or cardiac arrhythmia. The PTs selected for analysis are listed in Table 9. Table 8 displays signals scores with EBGM values >2.

Results:

Overall, no signals of Torsade or sudden death were detected.

All top signals were linked to bupropion. The top signal for bupropion with EBGM (EB05, EB95) values of 4.15 (4.0, 4.29) was convulsion, an AE reported in the approved bupropion prescribing information. The second top signal with EBGM (EB05, EB95) values of 3.54 (2.73, 4.52) was, electrocardiogram QRS complex prolonged. Another signal linked to ECG intervals with EBGM values > 2.0 was electrocardiograms repolarization abnormalities and bundle branch block. (Table 8)

By reviewing narratives for QRS prolonged and bundle branch block all cases were linked to bupropion overdose.

Table 8. EBGM values for Bupropion and Naltrexone and adverse event codes related to changes in ECG intervals duration or cardiac arrhythmia

Generic name	PT	HLT	HLGT	SOC	N	EBGM	EB05	EB95
Bupropion	Convulsion	Seizures and seizure disorders NEC	Seizures (incl subtypes)	Nerv	2225	4.15	4.00	4.29
Bupropion	Electrocardiogram QRS complex prolonged	ECG investigations	Cardiac and vascular investigations (excl enzyme tests)	Inv	42	3.54	2.73	4.52
Bupropion Slow Release	Convulsion	Seizures and seizure disorders NEC	Seizures (incl subtypes)	Nerv	14	2.58	1.64	3.89
Bupropion Slow Release	Palpitations	Cardiac signs and symptoms NEC	Cardiac disorder signs and symptoms	Card	9	2.45	1.40	4.05
Bupropion	Electrocardiogram repolarisation abnormality	ECG investigations	Cardiac and vascular investigations (excl enzyme tests)	Inv	6	2.30	1.16	4.18
Bupropion Slow Release	Electrocardiogram QRS complex prolonged	ECG investigations	Cardiac and vascular investigations (excl enzyme tests)	Inv	2	2.15	0.678	5.68
Bupropion	Bundle branch block	Cardiac conduction disorders	Cardiac arrhythmias	Card	14	2.06	1.31	3.10

Notes	
ID:	3711
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S) (v2)
Configuration description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As of date:	09/09/2010 00:00:00
Item variables:	Generic name, PT
Stratification variables:	Standard strata
Highest dimension:	2
Minimum count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base counts on cases:	Yes
Use "all drugs" comparator:	No
Apply Yates correction:	Yes
Stratify PRR and ROR:	No
Fill in hierarchy values:	Yes
Exclude single itemtypes:	Yes
Fit separate distributions:	Yes
Save intermediate files:	No
Created by:	Empirica Signal Administrator
Created on:	09/18/2010 07:05:50 EDT
User:	Monica Fiszman
Source database:	Source Data: CBAERS data from Extract provided by CBER as of 09/09/2010 00:00:00 loaded on 2010-09-16 07:58:08.0

Table 9. PTs selected for analysis

Dimension: 2 Selection Criteria: Generic name(Bupropion, Bupropion Extended Release, Bupropion Slow Release, Naltrexone) + PT(Accelerated idioventricular rhythm, Anomalous atrioventricular excitation, Arrhythmia, Arrhythmia supraventricular, Athletic heart syndrome, Atrial fibrillation, Atrial flutter, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular extrasystoles, Bifascicular block, Bradycardia, Bradycardia foetal, Bradycardia neonatal, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac arrest, Cardiotoxicity, Convulsion, Electrocardiogram PQ interval, Electrocardiogram PQ interval prolonged, Electrocardiogram PR interval, Electrocardiogram PR prolongation, Electrocardiogram PR shortened, Electrocardiogram Q wave abnormal, Electrocardiogram Q waves, Electrocardiogram Q waves normal, Electrocardiogram QRS complex, Electrocardiogram QRS complex prolonged, Electrocardiogram QRS complex shortened, Electrocardiogram QT interval, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Electrocardiogram QT shortened, Electrocardiogram RR interval prolonged, Electrocardiogram T wave abnormal, Electrocardiogram T wave amplitude decreased, Electrocardiogram T wave amplitude increased, Electrocardiogram T wave biphasic, Electrocardiogram T wave inversion, Electrocardiogram U wave inversion, Electrocardiogram U-wave abnormality, Electrocardiogram U-wave biphasic, Electrocardiogram abnormal, Electrocardiogram ambulatory abnormal, Electrocardiogram repolarisation abnormality, Heart rate, Heart rate abnormal, Heart rate decreased, Heart rate increased, Hypokalaemia, Hypomagnesaemia, Long QT syndrome, Palpitations, Presyncope, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Sudden cardiac death, Sudden death, Syncope, Tachyarrhythmia, Tachycardia, Torsade de pointes, Ventricular arrhythmia, Ventricular asystole, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia, Wolff-Parkinson-White syndrome) Where: EBGM > 2.0

SPONSOR'S PROPOSAL



(b) (4)

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

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

Date: August 18, 2010

To: Eileen Craig, MD
Medical Officer
Division of Metabolism and Endocrinology Products
Office of New Drugs

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Subject: Bupropion Naltrexone Concurrency Analysis

Drug Name(s): Contrave® (Bupropion/Naltrexone) extended release tablet

Application Type/Number: NDA 200-063

Applicant/sponsor: Orexigen

OSE RCM #: 2010-1257

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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EXECUTIVE SUMMARY

The Division of Metabolic and Endocrinology Drug Products (DMEP) is reviewing an NDA for a combination product (bupropion/naltrexone) for the treatment of obesity and requested utilization analyses from the Office of Surveillance and Epidemiology (OSE). An Advisory Committee meeting on the review of the safety and efficacy of this combination of drugs is expected in December 2010. This review provides an analysis of bupropion and naltrexone concurrency by age, analysis of outpatient dispensed prescriptions and projected number of patients filling a bupropion or naltrexone outpatient prescription by age, and an analysis of physician reports of diagnoses associated with the use of each product alone and with any additional therapy used to treat the same diagnosis.

National Outpatient Prescription Utilization Analysis

Bupropion dispensed prescriptions remained stable (approximately (b) (4) per year) from year 2005 ((b) (4) prescriptions) to year 2009 ((b) (4) prescriptions), a (b) (4). Across all years studied, bupropion prescriptions were primarily dispensed to patients aged (b) (4) years ((b) (4) %). The number of prescriptions dispensed to the (b) (4) year age group from year 2005 ((b) (4) prescriptions) to year 2009 ((b) (4) prescriptions) remained fairly stable ((b) (4) %). From January 2005 through May 2010, the (b) (4) of bupropion prescriptions was dispensed as the 150 mg strength ((b) (4) million prescriptions) followed by the 300 mg strength ((b) (4) million prescriptions).

Naltrexone dispensed prescriptions ((b) (4) % from year 2005 ((b) (4) prescriptions) to year 2009 ((b) (4) prescriptions) across all age groups. Prescriptions dispensed to patients aged (b) (4) years ((b) (4) % from (b) (4) in year 2005 to (b) (4) in year 2009 and across all years studied, naltrexone prescriptions were primarily dispensed to this age group ((b) (4) %). From January 2005 through May 2010, naltrexone 50 mg accounted for nearly (b) (4) % of naltrexone prescriptions

Nationally Projected Number of Outpatient Bupropion and Naltrexone Prescription Claims by Age Analysis

The overall total number of patients with a prescription claim for bupropion (b) (4) by around (b) (4) % from approximately (b) (4) million patients in year 2006 to approximately (b) (4) million patients in year 2009. During year 2009, of the (b) (4) million patients with a bupropion prescription claim, the majority (b) (4) % or (b) (4) patients) were aged (b) (4) years at time of the first prescription claim. This trend in age distribution was similar during each of the three previous calendar years.

The overall number of patients with a prescription claim for naltrexone (b) (4) by around (b) (4) % from approximately (b) (4) patients in year 2006 to approximately (b) (4) patients in year 2009. Patient counts with a naltrexone claim (b) (4) across all age groups from year 2006 to year 2009. During year 2009, of the (b) (4) patients with a naltrexone claim, the majority ((b) (4) % or (b) (4)) were patients aged (b) (4) years.

Concurrent Drug Analysis

Nationally projected number of patients was used to assess concurrency between patients with a claim for bupropion and a claim for naltrexone during each calendar year from 2006 to 2009.

Across all years studied, less than (b)(4)% of patients in all age groups with a bupropion claim had a concurrent claim for naltrexone. While, around (b)(4)% of patients in all age groups with a naltrexone claim had a concurrent claim for bupropion.

Across all years studied, for naltrexone patients with a concurrent bupropion claim, there was a greater percentage of concurrency (b)(4)% for patients aged (b)(4) years compared to other age groups (b)(4)% for ages (b)(4), and (b)(4) years).

Associated Diagnoses Analysis

According to office-based physician reports from January 2005 through May 2010, weight management, obesity and eating disorders diagnoses associated with the use of bupropion accounted for less than (b)(4)% of drug use mentions. There were no reports of diagnoses for weight management, obesity and eating disorders associated with the use naltrexone during the time period studied.

1 INTRODUCTION

The Division of Metabolic and Endocrinology Drug Products (DMEP) is reviewing NDA 200-063, Contrave[®] (bupropion/naltrexone) Extended-Release Tablets, for the treatment of obesity and weight management. As part of this NDA review, DMEP requested an analysis of drug utilization patterns for bupropion with naltrexone as monotherapy as well as concurrent use of bupropion with naltrexone during years 2006-2009. This review provides outpatient drug utilization patterns for bupropion and naltrexone in terms of projected number of outpatient dispensed prescriptions and projected number of patients stratified by patient age and by product strength from year 2005 to year to date May 2010. Physician reports of diagnoses associated with the use of each product alone and with any additional therapy used to treat the same diagnosis were also analyzed for the cumulative time period from year 2005 to year-to-date May 2010.

1.1 BACKGROUND

Orexigen submitted a 505(b)(2) New Drug Application (NDA) for Contrave[®], (bupropion/naltrexone) Extended-Release Tablet for the treatment of obesity and weight management. Naltrexone hydrochloride is an FDA approved mu-opioid receptor antagonist indicated for the treatment of opiate and alcohol dependence as monotherapy. Bupropion hydrochloride is an FDA approved norepinephrine and dopamine reuptake inhibitor indicated for the treatment of major depression and nicotine dependence.

Bupropion is available as brand and generic oral products. Brand products include Wellbutrin[®] which was approved December 1985; Wellbutrin[®] SR was approved October 1996; Zyban[®] was approved May 1997; Wellbutrin[®] XL was approved August 2003; and Aplenzin[®] was approved in April 2008. Naltrexone is available as brand and generic oral and intramuscular products. Brand products include Revia[®], which was approved in November 1984. Vivitrol[®], approved in April 2006, is the intramuscular formulation of naltrexone and was not included in this analysis.

2 METHODS AND MATERIALS

2.1 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

2.1.1 National Outpatient Prescription Utilization Analysis

SDI Vector One[®]: National (VONA) was used to examine nationally projected number of total dispensed prescriptions for bupropion or naltrexone by age and by strength.

2.1.2 Nationally Projected Number of Outpatient Bupropion and Naltrexone Prescription Claims by Age Analysis and Concurrent Drug Analysis

The Wolters Kluwer Source Lx[®] CPA (WKCPA) tool was used to examine episodes of concurrency for patients with a U.S. outpatient prescription claim for bupropion or naltrexone for a duration of at least one day during each calendar year 2006, 2007, 2008 and 2009 with a 90 day study look back period. The patient population was selected based on the occurrence of one bupropion or one naltrexone claim per year. An episode of concurrency is identified when a patient has overlapping therapy days with bupropion and naltrexone. A grace period of 50% was applied to prescription claims the end of days supply on a prescription claim for each product to compensate for under compliance and to determine continuation of therapy.

2.1.3 Associated Diagnoses Analysis

SDI's Physician's Drug and Diagnosis Audit[™] (PDDA) was used examine reports of diagnoses associated with the use of bupropion or one naltrexone alone and with any additional therapy used to treat the same diagnosis.

2.2 PRODUCTS INCLUDED

For the concurrent drug analysis, we included all bupropion brand and generic products and all oral naltrexone brand and generic products (excluding the brand Vivitrol[®] intramuscular naltrexone).

3 RESULTS: DATA

3.1 NATIONAL OUTPATIENT PRESCRIPTION UTILIZATION ANALYSIS

3.1.1 Nationally Projected Number of Outpatient Dispensed Bupropion and Naltrexone Prescriptions by Age (Table 1)

(b) (4)



(b) (4)

3.1.2 Nationally Projected Number of Outpatient Dispensed Bupropion and Naltrexone Prescriptions by Strength (Table 2)

(b) (4)

3.2 NATIONALLY PROJECTED NUMBER OF OUTPATIENT BUPROPION AND NALTREXONE PRESCRIPTION CLAIMS BY AGE (TABLE 3)

(b) (4)

3.3 CONCURRENT DRUG ANALYSIS USING PRESCRIPTION CLAIMS (TABLE 4)

4 DISCUSSION

The findings from this consult should be interpreted in the context of the known limitations of the databases used.

We estimated that these products are distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Unique patient counts from the Wolters Kluwer Source Lx® CPA database may **not** be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Therefore, summing patients across years is not advisable and will result in overestimates of patient counts. Data is from commercially insured,

Medicare Part D, Medicaid, and Cash payors, thus the elderly population (age 65+ years) is adequately represented.

SDI's Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data estimates unstable, particularly if use is not common in the pediatric population. SDI recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

5 CONCLUSION

In year 2009, an estimated (b) (4) bupropion and (b) (4) prescriptions were dispensed nationally in the outpatient retail pharmacy settings and an estimated (b) (4) patients filled bupropion prescriptions and (b) (4) patients filled naltrexone prescriptions. The majority of prescriptions for both drugs were primarily dispensed to patients aged (b) (4) years. The (b) (4) bupropion prescriptions were dispensed as the 150 mg strength and naltrexone was (b) (4) the 50 mg strength.

The concurrent drug analyses revealed (b) (4) rates of naltrexone use among patients with bupropion prescription claim; less than (b) (4) % of patients in all age groups. Conversely, there was a (b) (4) % rate of bupropion concurrency among patients with a naltrexone claim. However, according to office-based physician reports, weight control diagnoses associated with the use of bupropion represents a relatively small proportion of the use. There were no reports of diagnoses for weight control associated with the use naltrexone during the time period studied.

CONCURRENCE

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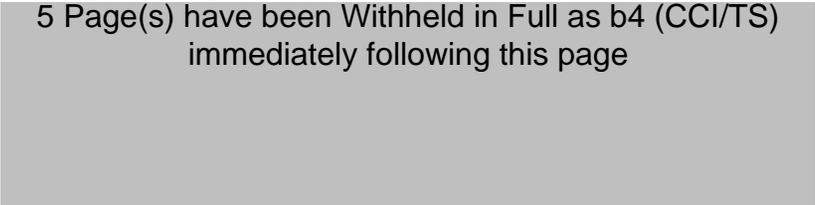
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APPENDICES

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APPENDIX 2 – DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Wolters Kluwer SOURCE Lx®

Wolters Kluwer Health's Source® Lx database a longitudinal patient data source which capture adjudicated claims across the United States from a mix of prescription claims from commercial plans, Medicare Part D plans, Cash and Medicaid claims. The database contains approximately 4.8 billion paid, non-reversed prescriptions claims linked to over 172 million unique prescription patients of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents 27,000 pharmacies, 1,000 hospitals, 800 clinics/outpatient facilities, and 80,000 physician practices.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Physician Drug & Diagnosis Audit (PDDA)

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and

trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200063	ORIG-1	OREXIGEN THERAPEUTICS INC	CONTRAVE® (Naltrexone HCl and Bupropion HCl)

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/s/

BRENDA V BORDERS-HEMPHILL

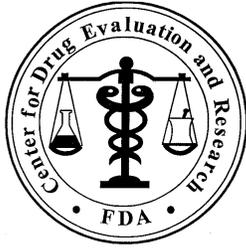
08/19/2010

This document has been database vendor cleared and is the revised version update with corrected patient counts (total changed from nonconcurrent only counts to concurrent plus nonconcurrent patient counts)

AMARILYS VEGA

08/19/2010

Signed for: Solomon Iyasu



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

Date: August 17, 2010

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Subject: AERS Review

Drug Name(s): Bupropion/Naltrexone (Contrave)

Application Type/Number: NDA 200-063

Applicant/sponsor: Orexigen Therapeutics

OSE RCM #: 2010-926

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1 INTRODUCTION

This review provides an analysis of AERS reports associated with bupropion (Wellbutrin, Zyban, Aplenzin) and naltrexone (Revia, Vivitrol). This analysis focuses on reports describing concurrent use of bupropion and naltrexone, but also provides an overview of the U.S. serious reports associated with bupropion and naltrexone as single agents. The Division of Metabolic and Endocrine Products (DMEP) requested this review to assist in their evaluation of NDA 200-063 (Contrave), a combination product of bupropion and naltrexone for the management of weight loss. An Advisory Committee meeting is scheduled for December 7, 2010 for considering approval of the combination product for weight management.

DMEP's preliminary analysis of the Contrave NDA identified the following relevant safety issues:

1. Cardiac Disorders (myocardial infarction, stroke, coronary revascularization procedure, palpitations, increased blood pressure and or pulse)
2. Ear and Labyrinth Disorders (tinnitus)
3. Gastrointestinal Disorders (nausea, constipation, vomiting, dry mouth, abdominal pain, dysgeusia)
4. Hepatobiliary Disorders (hepatotoxicity and gallbladder disease)
5. Immune System Disorders (hypersensitivity)
6. Musculoskeletal and Connective Tissue Disorders (joint and muscle pain)
7. Nervous System Disorders (seizures, cognitive impairment, dizziness, syncope, headache, tremor, dysgeusia)
8. Psychiatric Disorders (suicidality, depression, anxiety, sleep disorders, agitation)
9. Renal and Urologic Disorders (renal impairment, increase in serum creatinine)
10. Skin and Subcutaneous Tissue Disorders (skin rash, hyperhidrosis)
11. Vascular Disorders (hot flush)

2 BACKGROUND

This section provides the proposed indication and dosage for bupropion/naltrexone (Contrave), and known safety information for bupropion and naltrexone as single agents.

2.1 BUPROPION/NALTREXONE (CONTRAVE)

Orexigen Therapeutics, the sponsor of Contrave (bupropion/naltrexone), is seeking an indication for the treatment of obesity and weight management, including both weight loss and maintenance of weight loss for patients with an initial BMI ≥ 30 kg/m² or a BMI ≥ 27 kg/m² with one or more risk factors (diabetes, dyslipidemia, or hypertension). The proposed Contrave dosage forms are 90 mg/4 mg and 90 mg/8 mg tablets (extended release) for a recommended maintenance dosage of two tablets twice daily (360 mg of bupropion/32 mg of naltrexone total daily dose).

2.2 BUPROPION (WELLBUTRIN, ZYBAN, APLENZIN^{*})^{1,2,3,4}

Bupropion, a relatively weak inhibitor of norepinephrine and dopamine reuptake, was initially approved by FDA in 1985 for the treatment of depression. Since 1985, bupropion has also been approved for use in the management of smoking cessation (Zyban), major depressive disorder (Wellbutrin, Wellbutrin XL, Aplenzin), and seasonal affective disorder (Wellbutrin XL). The usual target dose is 300 mg daily (maximum of 450 mg daily). Bupropion, like other antidepressants, has a boxed warning for suicidality, and a Risk Evaluation and Mitigation Strategy (Medication Guide) for suicidality and seizures.

Safety concerns with bupropion center around the 1) dose-related noradrenergic and dopaminergic effects that are primarily neuropsychiatric (seizures, suicidality, mood changes) and cardiovascular, and 2) idiosyncratic reactions such as allergic reactions and liver injury.

The bupropion labeling advises (WARNINGS AND PRECAUTIONS) of the following:

- Clinical worsening and suicide risk in treating psychiatric disorders (closely monitor patients, particularly children, adolescents and young adults)
- Neuropsychiatric symptoms (serious mood changes, including depression, psychosis, mania, anxiety, and completed suicide) with smoking cessation treatment (events occur in patients with and without psychiatric disease)
- Screen patients for bipolar disorder (treatment with an antidepressant may precipitate a mixed and or manic episode in patients at risk for bipolar disorder)
- Do not use multiple bupropion-containing products
- Seizures:
 - Risk of seizure strongly associated with dose; ~ 0.4 percent of patients treated at doses up to 450 mg/day experienced a seizure; the seizure incidence increases almost tenfold between 450 and 600 mg per day
 - Risk of seizure is related to 1) patient factors [history of prior seizures or head trauma], 2) clinical situations [excessive use of alcohol or sedatives, and patients with diabetes treated with oral hypoglycemics or insulin] and 3) concomitant use of medications known to lower the seizure threshold [antipsychotics, other antidepressants, etc)
 - To reduce risk of seizure, total bupropion daily dose should not exceed 450 mg; each single dose should not exceed 150 mg; increase dose gradually

^{*} Aplenzin contains the hydrobromide form of bupropion. Wellbutrin, Wellbutrin XL, and Zyban contain the hydrochloride form of bupropion.

Bupropion WARNINGS AND PRECAUTIONS continued:

- Hepatotoxicity (animal data suggests an increase in the incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy)
- Neuropsychiatric symptoms, including agitation, insomnia, psychosis, confusion, mania (symptoms sometimes severe and require treatment with sedative/hypnotic drugs or discontinuation of bupropion)
- Weight loss (28 percent of patients treated with bupropion lost > 5 pounds)
- Allergic reactions, including rare postmarket reports of Stevens-Johnson syndrome and anaphylactic shock
- Cardiovascular events (severe hypertension requiring acute treatment reported in patients with or without evidence of pre-existing hypertension; use in caution in patients with history of myocardial infarction or unstable heart disease)
- Hepatic impairment (use with caution in patients with hepatic impairment; extreme caution in patients with severe hepatic cirrhosis)
- Renal impairment (bupropion and associated metabolites may accumulate in patients with renal impairment)
- Drug interactions – bupropion metabolized by CYP2B6, and inhibits CYP2D6; caution using bupropion with drugs known to lower the seizure threshold
- Pregnancy Class C

Bupropion is CONTRAINDICATED in patients:

- With a seizure disorder
- Treated with other medications containing bupropion because the incidence of seizures is dose dependent.
- A current or prior diagnosis of bulimia or anorexia nervosa (higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion)
- Abruptly discontinuing alcohol or sedatives (including benzodiazepines)
- Taking a monoamine oxidase inhibitor

Bupropion Reports in AERS

Serious adverse events associated with bupropion that are frequently reported to AERS (listed in APPENDIX I) are consistent with those described in the bupropion labeling. Of note, between marketing and January 1, 2002 (cutoff date chosen because of stimulated reporting associated with communications regarding an increased risk of suicidality with antidepressant use), the top ten most frequently reported events are Convulsions, Urticaria, Grand Mal Convulsions, Dermatitis, Pruritus, Dyspnea, Tremor, Dizziness, Overdose (intentional and unintentional), and Drug Interaction.

Bupropion Deaths

AERS contains 166 reports of death associated with bupropion that were reported to FDA between the initial marketing approval in 1985 and January 1, 2002 (cutoff date chosen because of stimulated reporting associated with communications regarding an increased risk of suicidality with antidepressant use). The three most frequently reported events associated with a bupropion death are Intentional Overdose or Suicide (80 reports), Cardiac Arrhythmia (18 reports), and Seizure (14 reports). APPENDIX II lists the bupropion reports of death by System Organ Class.

2.3 NALTREXONE (REVIA, VIVITROL)⁵⁶

Naltrexone, initially approved by FDA in 1984, is a reversible opioid antagonist approved for use in the management of alcohol dependence and blockade of the effects of exogenously administered opioids. Naltrexone is available both as an oral tablet (ReVia) and injection (Vivitrol). The recommended oral naltrexone dose is 50 mg once daily, which will block the pharmacologic effects of 25 mg of intravenously administered heroin for up to 24 hours.

Naltrexone has high affinity for mu opioid binding sites, and in the absence of an agonist drug may have limited effects. The naltrexone labeling advises (WARNINGS AND PRECAUTIONS) the following:

- Naltrexone may cause hepatocellular injury, particularly at higher doses (margin of separation between the safe dose of naltrexone and the dose causing liver injury is 5-fold or less; no reports of liver failure have been reported)
- Naltrexone is contraindicated in patients with acute hepatitis or liver failure; use with caution in patients with active liver disease
- Injection site reactions (with Vivitrol, the injectable naltrexone formulation) may be severe (including surgical excision of necrotic tissue)
- Eosinophilic pneumonia (reported in clinical trials with Vivitrol, the injectable naltrexone formulation)
- Patients must be opioid-free for at least 7-10 days before starting naltrexone (consider to administer naloxone challenge test to confirm patient is opioid-free)
- Attempting to overcome naltrexone blockade by administering large amounts of exogenous opioids may lead to a fatal opioid overdose
- Patients with history of opioid use may be more sensitive to lower doses of opioids after naltrexone is discontinued
- If reversal of naltrexone blockade is required, consider regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics, or general anesthesia
- Accidental ingestion of naltrexone by opioid-dependent individuals has resulted in severe opioid withdrawal syndromes
- Caution in patients with renal impairment (naltrexone and its metabolite are excreted primarily in the urine)
- Caution in patients with liver disease (naltrexone AUC increased 5- and 10-fold in patients with compensated and decompensated liver cirrhosis)
- Naltrexone does not abate risk of depression or suicide (risk of suicide increased in patients with substance abuse; depression more common in patients treated with Vivitrol, the injectable naltrexone formulation)
- Pregnancy Class C

Naltrexone is CONTRAINDICATED in patients:

- Receiving opioid analgesics
- Dependent on opioids
- In acute opioid withdrawal
- Who have failed the naloxone challenge test or have a positive urine screen for opioids
- With acute hepatitis or liver failure

Naltrexone Reports in AERS

Serious adverse events associated with naltrexone that are frequently reported to AERS (listed in APPENDIX III) are consistent with the naltrexone labeling. Of note, the top ten most frequently reported events are Vomiting, Nausea, Diarrhea, Death[†], Injection Site Pain, Depression, Drug Ineffective, Drug Withdrawal Syndrome, Condition Aggravated, and Drug Interaction.

Naltrexone Deaths

Since marketing through January 1, 2010, AERS contains 52 naltrexone reports associated with death. The three most frequently reported events associated with a naltrexone death are Suicide, Overdose (unclear if intentional or accidental), and Rapid or Ultra Rapid Detoxification. APPENDIX IV lists the naltrexone reports of death by System Organ Class.

[†] Death is generally reported as an outcome. However, the term, Death is used as a coding term when there is no adverse event reported.

3 METHODS

3.1 AERS SEARCH STRATEGY

AERS was searched on July 5, 2010 using the search criteria in Table 1 below.

<i>Product(s):</i>	Interaction Search Product 1: Bupropion (Wellbutrin, Zyban, Aplenzin) Product 2: Naltrexone (ReVia, Vivitrol) Products-Trade Name: Contrave (separate search)
<i>Search Terms:</i>	All
<i>Search Dates:</i>	Marketing approval for each product through January 1, 2010
<i>Countries:</i>	All (United States & foreign)
<i>Ages:</i>	All
<i>Combination Products:</i>	Yes
<i>Concomitant Products:</i>	Yes
<i>Reason for Use:</i>	All
<i>Outcome:</i>	All (Serious and Nonserious)

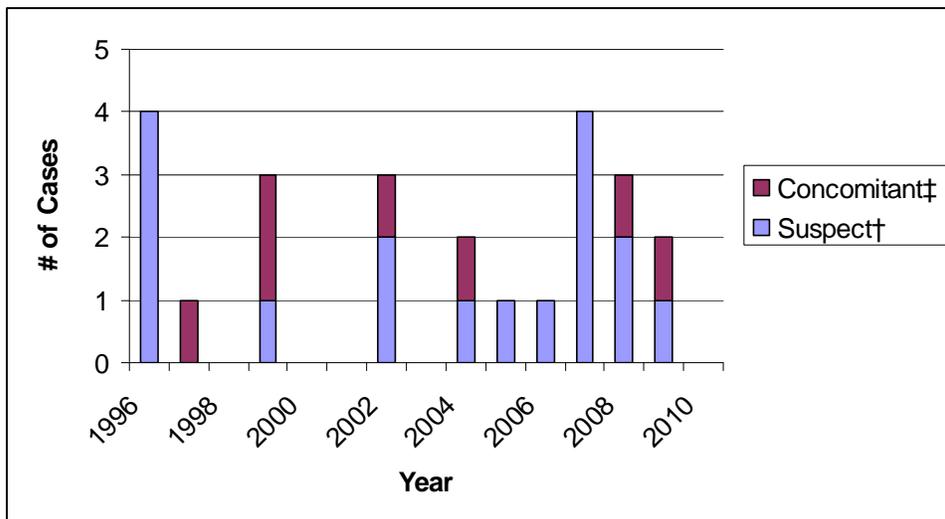
3.2 CASE SELECTION

We limited the AERS reports to spontaneous reports involving a patient on both bupropion and naltrexone. The search strategy in Section 3.1 identified 29 unique cases (US: 26, Foreign: 3), of which we excluded five cases because they were not spontaneous reports (legal reports: 4, solicited: 1). APPENDIX V lists the five excluded cases by ISR number.

4 RESULTS

Using the search criteria and case selection described in Section 3 (Methods), AERS contains 24 cases (US: 21, Foreign: 3) associated with concurrent use of bupropion and naltrexone. Seventeen of the twenty-four cases reported bupropion and or naltrexone as a suspect drug in causing the adverse event, and seven cases reported bupropion and naltrexone as concomitant drugs. No deaths were reported. The 24 cases are presented by FDA receipt year in Figure 1.

Figure 1. AERS Cases (Serious and Nonserious, U.S. and foreign) With Concurrent Use of Bupropion and Naltrexone, by Reported Suspect Drug (n=17) or As Concomitant Drug (n=7) and FDA Receipt Year, Marketing through January 1, 2010



Suspect=bupropion and or naltrexone was identified by the reporter as “suspect” in causing the adverse event

Concomitant=bupropion and naltrexone were listed in the report, but not suspected by the reporter as causing the adverse event

Table 4 presents the characteristics of the 24 cases involving concurrent use of bupropion and naltrexone. None of the cases suggested bupropion and or naltrexone were prescribed for weight management. None of the cases implicated both bupropion and naltrexone as suspect in having caused the adverse event. However, attribution was difficult because of the concomitant use of multiple medications, and presence of underlying drug and or alcohol abuse. APPENDIX IV provides a brief description of the 24 cases.

Table 4. Characteristics of AERS Cases (Serious and Nonserious) Associated With Concurrent Use of Bupropion and Naltrexone (n=24). Source: AERS, Marketing Through January 1, 2010		
Characteristic		
Reporting Country	United States	21
	Foreign	3
Age (yrs) Median: 44 Range: 14- 60 n=24	<30 yrs	6
	30-39 yrs	3
	40-49 yrs	11
	50-59 yrs	3
	60+ years	1
	Age not reported	--
Gender Percent Female: 50	Female	12
	Male	12
Weight (kg) Median: 74 Range: 42 - 102 n=10	40-59	1
	60-79	5
	80-100	3
	>100 kg	1
	Weight not reported	14
Reported Reason for Use	Mental Health Disorder	6
	Drug and or Alcohol Abuse	5
	Smoking Cessation	4
	Reason for Use Not Reported	9

Table 4. Characteristics of AERS Cases (Serious and Nonserious) Associated With Concurrent Use of Bupropion and Naltrexone (n=24). Source: AERS, Marketing Through January 1, 2010
Reported Suspect Drug*: Bupropion (6), Naltrexone (11), Other (7)
<p>Reported Events For the 6 Cases Listing BUPROPION as the Suspect Drug* (brand name, dose, and time to event or duration of therapy)</p> <p>Acute Hepatitis (bupropion 300 mg daily x 1 month)</p> <p>Anxiety, Suicidal Ideation, Mood Change (Zyban 150 mg x 4 months)</p> <p>Rash, Sore Throat and Tongue (Wellbutrin XL 150 mg daily x 2 weeks)</p> <p>Amenorrhea (Wellbutrin SR 100 mg BID x unknown duration)</p> <p>Swollen Hands, Itching, Aggravation, Hyperactivity, Blurred Vision (Wellbutrin 150 mg BID x 1 wk)</p> <p>Headache, Nausea, Dry Mouth, Leg Twitching (Zyban 150 mg daily or BID x 3 months)</p>
<p>Reported Events For the 11 Cases Listing NALTREXONE as the Suspect Drug* (brand name, dose and duration of therapy or time to event)</p> <p>Abnormal Feeling, "Dilated Pupils," Abdominal Pain, Insomnia (Revia 50 mg daily x 1 dose)</p> <p>Weight Loss and Anorexia (Revia 25 mg BID x 4 months)</p> <p>Bone Pain, Abdominal Pain, Nausea, Insomnia (Revia 50 mg daily x 2 days)</p> <p>Agitation, "Feeling Uptight and Excited" (Revia 50 mg daily x 2 months)</p> <p>Tendonitis, Medial Epicondylitis, Back Pain (Revia 50 mg daily x 1 month)</p> <p>Pancreatic Cyst (Revia 75 mg daily x 9 months)</p> <p>Cancer, Laryngeal (Vivitrol unk dose x 6 months)</p> <p>Pneumonia and Sepsis (Vivitrol 380 mg IM monthly, 2 days after 3rd injection)</p> <p>Blurred Vision, "Seizure," Vomiting, "Coma," "Pneumonia" (Vivitrol 380 mg IM x 1 dose)</p> <p>Dizziness, Respiratory Nausea, Depression, Delirium, Aggression (Vivitrol 380 mg IM x 1 dose)</p> <p>Injection Site Reaction (Vivitrol 380 mg IM monthly x 2 months)</p>
<p>Reported Events For the 7 Cases Listing Bupropion/Naltrexone As Concomitant Drugs (suspect drug listed in parentheses)</p> <p>Premature Ejaculation (methylphenidate)</p> <p>Akathisia (thioridazine)</p> <p>Urine Drug Screen Positive (venlafaxine)</p> <p>Hyponatremia (oxcarbazepine)</p> <p>In Utero Exposure (lithium)</p> <p>Worsening Depression (varenicline)</p> <p>"Swollen" Tongue, Mouth and Lips; Memory Impairment; Mood Change (lisdexamfetamine)</p>

* Suspect Drug=the drug was suspected by reporter to have caused the adverse event

Table 4. Characteristics of AERS Cases (Serious and Nonserious) Associated With Concurrent Use of Bupropion and Naltrexone (n=24). Source: AERS, Marketing Through January 1, 2010

Reported Medical History†

- Alcohol/Drug Abuse or Addiction (10)
- Mood Disorder (depression, bipolar, panic disorder, self injurious behaviors) (10)
- Attention Deficit Hyperactivity Disorder (2)
- Cardiac Disorder (HTN, arrhythmia, or taking cardiac drugs) (4)
- Respiratory Disorder (asthma, COPD, smoking) (5)
- Medical history not reported (5)

Reported Medication History†

- Antiepileptics (VPA, gabapentin, zonisamide, topiramate, lamotrigine): 9
- Antidepressants (SSRI, SNRI, TCA): 5
- Benzodiazepines: 4
- Antipsychotics: 4
- Lithium: 1
- Cardiac medications (beta blocker, ARB, terazosin): 4
- Trazodone: 3
- Other: PPI (4), buspirone (3), H2Blocker (1), Chantix (1), opioid (1)

†Numbers may not sum because cases may report more than one comorbidity or concurrent medication

5 DISCUSSION

Given two-third of adults in the United States are either overweight or obese,⁷ weight loss products, such as Contrave, may have widespread exposure, and the potential for associated safety issues must be considered.

Although the Contrave labeling defines the intended population (overweight or obese), other characteristics of the population using Contrave is not known. Thus, there exists a potential for exposure to women of childbearing age, and significant drug interactions (bupropion is metabolized by CYP2B6 and inhibits CYP2D6). This review also identified other important safety concerns (described in the bupropion and or naltrexone labelings) that include seizures, suicidality, cardiovascular events, and liver injury. Further, the safety profile associated with long term use of Contrave is not known.

As part of the Contrave NDA, the sponsor submitted a postmarket safety analysis of bupropion and naltrexone.⁸ The sponsor concluded, “key safety signals including the risk of suicidality with antidepressants, seizures with bupropion, and use of naltrexone with opiates are well-described in the prescribing information.” However, the sponsor’s analysis and conclusions were based on AERS line listings and data mining algorithms, which are insufficient for FDA to have a comprehensive understanding of each product’s safety profile.

6 CONCLUSIONS AND RECOMMENDATIONS

Both bupropion and naltrexone have been approved as single ingredient products in the United States for more than 20 years. However, little is known about the postmarket safety profile when bupropion and naltrexone are used for weight management. Contrave could have widespread use, and the potential for safety issues (including seizures, suicidality, and cardiovascular events) cannot be dismissed.

Approval of Contrave, based on benefit and risk, should take into account the safety profile not only of the combination product, but the individual components as well. The sponsor submitted a Summary of Clinical Safety that included a postmarket analysis of bupropion and naltrexone. However, the analysis is insufficient for FDA to have a comprehensive understanding of Contrave’s safety profile when used in the targeted overweight or obese population.

The Division of Pharmacovigilance (DPV) recommends DMEP consider requesting the sponsor submit to FDA for review, an integrated safety summary (ISS) that contains separate sections for bupropion and naltrexone, and is organized by targeted safety topics. For bupropion, the serious targeted safety topics include seizures, cardiac arrhythmias, hypertension, stroke, suicidality and other psychiatric disorders, cognitive impairment, use in special patient populations (including exposure during pregnancy), misuse (including

overdose), allergic reactions, drug interactions (including use with other bupropion-containing products, drugs that lower the seizure threshold, and drugs metabolized by CYP2D6), and long term exposure. For naltrexone, the targeted safety topics include, but are not limited to, use in special patient populations (including exposure during pregnancy), drug interactions (including opioids), overdose, hypersensitivity, and long term exposure.

For each of these drug-specific safety topics, the sponsor would consider postmarket reports, clinical trial data, and worldwide literature to provide the following information (separately) for naltrexone and bupropion in an ISS:

1. Introduction
 - Description of safety topic
 - Labeling relative to the safety topic
2. Background
 - Epidemiology
 - Possible causative agents
 - Other relevant clinical and nonclinical information
3. Experience (with the drug and safety topic of interest)
 - AERS or other postmarket reports
 - Fatalities (tabular summary and narrative descriptions)
 - Serious nonfatal cases
4. Review of Literature
5. Summary and Conclusions
6. References

[Redacted content]

¹ GlaxoSmithKline. Wellbutrin (bupropion hydrochloride) prescribing information. Greenville, NC. 2009.

² GlaxoSmithKline. Zyban (bupropion hydrochloride, sustained-release tablets) prescribing information. Greenville, NC. 2009.

³ GlaxoSmithKline. Wellbutrin XL (bupropion hydrochloride, extended-release tablets) prescribing information. Greenville, NC. 2009.

⁴ Sanofi Aventis. Aplenzin (bupropion hydrobromide, extended-release tablets) prescribing information. Bridgewater, NJ. 2009.

⁵ Alkermes, Inc. Vivitrol (naltrexone for extended release injectable suspension) prescribing information. Cambridge, MA. 2009.

⁶ Dupont Pharma. Revia (naltrexone hydrochloride tablets) prescribing information. 1999.

⁷ Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA*. 2010;303(3):235-241.

⁸ King A, Olesen A, Garrard E for the Drug Safety Alliance Inc. A post-marketing adverse drug event profile: bupropion and naltrexone (prepared for Orexigen Therapeutics, Inc.). 2010 Mar 9; 82 p.

APPENDIX I. Bupropion: Frequently Reported Adverse Events

Top 25 Serious Adverse Events (Crude Counts) Reported with BUPROPION, Organized by System Organ Class (SOC) and Preferred Term. Source: AERS, U.S. Cases, Marketing Approval in 1985 Through January 1, 2002*

SOC	Preferred Terms (crude counts)	Total Counts for SOC
Gastrointestinal Disorders		
	Nausea (91), Vomiting (81)	172
General Disorders and Administration Site Disorders		
	Drug Interaction (102), Chest Pain (94), Pyrexia (93), Facial Edema (75)	364
Immune System Disorders		
	Hypersensitivity (108)	108
Injury, Poisoning, and Procedural Complications		
	Intentional Overdose (120), Overdose (107)	227
Musculoskeletal and Connective Tissue Disorders		
	Arthralgia (86)	86
Nervous System Disorders		
	Convulsion (550), Grand Mal Convulsion (179), Tremor (130), Dizziness (123), Headache (103), Amnesia (73)	1158
Psychiatric Disorders		
	Insomnia (94), Confusional State (92), Depression (82), Anxiety (80), Agitation (75)	423
Respiratory, Thoracic and Mediastinal Disorders		
	Dyspnea (158)	158
Skin and Subcutaneous Disorders		
	Urticaria (274), Dermatitis (179), Pruritus (177)	630

*AERS was searched on July 6, 2010 for bupropion reports (U.S. serious only) using the generic (bupropion) and brand names (Wellbutrin, Zyban, Aplenzin). The cut off date was January 1, 2002 (cutoff date chosen because of stimulated reporting associated with communications regarding an increased risk of suicidality with antidepressant use).

APPENDIX II. Listing of U.S. Bupropion Deaths by System Organ Class (n=166)*

Reported Event Associated with Death By System Organ Class (SOC) (number of AERS reports)
Cardiac Disorder (19) Myocardial Infarction (6), Cardiac Arrest (5), Arrhythmia (4), Sudden Death (2), Left Ventricular Hypertrophy (1), Cardiomyopathy (1)
Hepatobiliary Disorders (2) Acute Liver Failure (1), Acute Hepatotoxicity (1)
Injury Poisoning and Procedural Complications (21) Overdose, Unknown if Accidental or Unintentional (16), Accidental Overdose (1), Post-Surgical Procedure (2), MVA (1), Medication Error (1)
Nervous System Disorders (18) Seizures (14) Cerebrovascular Accident (1), Neuroleptic Malignant Syndrome (1), Parkinsons disease (1), Cerebral Angitis (1)
Psychiatric Disorders (63) Intentional Overdose or Suicide (63)
Skin and Subcutaneous Tissue Disorders (1) Toxic Epidermal Necrosis (1)
Other SOC (14) In Utero Exposure (7) Respiratory, Thoracic and Mediastinal Disorders (3), Neoplasm, Cervical (1), Sepsis with ESRD(1), Airway Obstruction (1), Hyponatremia (1)
Unknown (28)

*AERS was searched on July 6, 2010 for bupropion reports (U.S. serious only) using the generic and brand names. The cut off date was January 1, 2002 (cutoff date chosen because of stimulated reporting associated with communications regarding an increased risk of suicidality with antidepressant use).

APPENDIX III. Naltrexone: Frequently Reported Adverse Events

Top 25 Serious Adverse Events Reported with NALTREXONE, Organized by System Organ Class (SOC) and Preferred Term. Source: AERS, U.S. Cases, Marketing approval in 1984 through January 1, 2010.*

SOC	Preferred Terms (crude counts)	Crude Counts
Gastrointestinal Disorders	Vomiting (29), Nausea (28), Diarrhea (21)	78
General Disorders and Administration Site Disorders	Death (21), Injection Site Pain (20), Drug Ineffective (19), Drug Withdrawal Syndrome (18), Condition Aggravated (17), Drug Interaction (17), Asthenia (11), Injection Site Reaction (11), Pain (11)	145
Musculoskeletal and Connective Tissue Disorders	Myalgia (11)	11
Nervous System Disorders	Convulsion (16), Dizziness (12)	28
Psychiatric Disorders	Depression (19), Agitation (14), Anxiety (14), Drug Dependence (14), Completed Suicide (13), Hallucination (11), Suicidal Ideation (11), Suicide Attempt (11), Alcohol Withdrawal Syndrome (10)	117

*AERS was searched on July 6, 2010 for naltrexone reports (U.S. serious only) using the generic (naltrexone) and brand names (ReVia, Vivitrol). The cut off date was January 1, 2010.

APPENDIX IV. Listing of U.S. Naltrexone Deaths by System Organ Class (SOC) (n=52)*

Reported Event Associated with Death By System Organ Class (number of AERS reports)
Cardiac Disorders (3) Arrhythmia (3)
Hepatobiliary Disorders (2) Liver Injury (2)
Injury, Poisoning, and Procedural Complications (18) Rapid or Ultra Rapid Detoxification with Naltrexone (8, of which 7 were associated with subcutaneous naltrexone implant) Overdose, unclear if intentional or accidental (8) Hyperthermia or Head Trauma Secondary to Alcohol Abuse (2)
Psychiatric Disorders (7) Suicide (7)
Respiratory, Thoracic, and Mediastinal Disorders (2) Respiratory Arrest (2)
Other (7) Cancer (4), GI Bleed (2), Pancreatitis (1)
Unknown (12)

*AERS was searched on July 6, 2010 for naltrexone reports (U.S. serious only) using the generic (naltrexone) and brand names (ReVia, Vivitrol). The cut off date was January 1, 2010.

APPENDIX V. Excluded Cases (n=5)

ISR # Source RCV Yr	Age (yr) Gender	Reported Suspect Drug	Reported Event	Reason for Exclusion
4273110 US 2003	30 Female	Paroxetine (Paxil)	Withdrawal symptoms	Attorney report
6194597 US 2009	24 Male	Quetiapine (Seroquel), olanzapine (Zyprexa)	Suicidality, MI, LVH	Attorney report
6271935 US 2007	34 Female	Quetiapine (Seroquel), olanzapine (Zyprexa)	Pancreatitis	Attorney report
6371601 US 2008	38 Female	Quetiapine (Seroquel)	Pancreatitis	Attorney report
6322643 US 2009	62 Male	Niacin (Niaspan)	Flushing	Solicited report

APPENDIX VI. Concurrent Use Cases (n=24)

ISR # Source RCV Yr	Age (yr) Gender	Reported Suspect Drug	Reported Event	PMH/ Concurrent Drugs	Outcome
1684232 US 1996	20 Female	Naltrexone (ReVia) 50 mg QD	"Feeling Weird," "Dilated Pupils," Stomachache, Insomnia	Opioid addiction/ bupropion (Wellbutrin)	Unknown
1684469 US 1996	14 Female	Naltrexone (ReVia) 25 mg BID (inc from 12.5 mg QD)	Weight Loss, Anorexia	Self injurious behavior, ADHD, seizure disorder/ valproic acid, bupropion (Wellbutrin)	Methylphenidate DC; not yet recovered
1845629 US 1996	37 Male	Naltrexone (ReVia) 50 mg QD	Bone Pain, Stomach Cramps, Nausea, Insomnia	Opioid addiction/ bupropion (Wellbutrin), amitriptyline	Unknown
1854107 US 1996	48 Male	Naltrexone (ReVia) 50 mg QD	Agitation, "Feeling of Uptight and Excited"	Alcoholism, Depression/ bupropion (Wellbutrin)	Naltrexone DC and "patient returned to normal"
3332428 US 1999	44 Male	Bupropion (Zyban) 150 mg QD or BID	HA, Nausea, Dry Mouth, Leg Twitching	Smoking/ trazodone, clonazepam, ranitidine, naltrexone	Bupropion continued, events unresolved
4019004 US 2002	22 Male	Naltrexone (ReVia) 50 mg QD	Tendonitis, Back Pain, Medical Epicondylitis	Drug abuse/ valproic acid, bupropion (Wellbutrin SR), risperidone	Symptoms improved by "about 30 %;" Unclear if naltrexone continued
4019006 US 2002	45 Female	Naltrexone (ReVia) 75 mg QD	Pancreatic Cyst	Alcoholism, depression, GI ulcer NOS, pancreatitis/ bupropion (Wellbutrin SR)	Continuing naltrexone, but "will be tapered off"

ISR # Source RCV Yr	Age (yr) Gender	Reported Suspect Drug	Reported Event	PMH/ Concurrent Drugs	Outcome
4270112 US 2004	42 Male	Bupropion (Wellbutrin) 150 mg BID	Swollen Hands, Itching, Irritation, Aggravation, Blurred Vision, Hyperactivity	Depression, smoking/ naltrexone NOS	Bupropion DC; events continued
4839744 US 2005	24 Female	Bupropion (Wellbutrin SR) 100 mg BID	Amenorrhea	Depression, cocaine abuse, bipolar/ naltrexone, risperidone, buspirone, topiramate	Bupropion continued, amenorrhea unresolved
5168225 CA 2006	60 Female	Bupropion (Wellbutrin XL) 150 mg QD	Rash, Sore Throat, Sore Tongue	---/ fluoxetine 20 mg TIW, losartan 50 mg BID, imiquimod, naltrexone 50 mg QD, celecoxib 200 mg QD, lansoprazole 30 mg QD, oxazepam 15 mg QD, steroid inhaler	Bupropion DC; treated in ER with diphenhydramine; events improved
5261930 US 2007	52 Male	Naltrexone (Vivitrol)	Laryngeal Cancer	Alcoholism, COPD, HTN, laryngeal CA/ bupropion (Wellbutrin), rosuvastatin, ramipril, Advair, baclofen, ondansetron, chemotherapy NOS	"Died of sepsis secondary to becoming immunocompromised following chemotherapy"
5298490 US 2007	43 Male	Naltrexone (Vivitrol) 380 mg IM QM	Pneumonia, Sepsis	--- bupropion (Wellbutrin XL), Chantix	Naltrexone and bupropion DC; hospitalized and recovered
5343687 US 2007	48 Male	Naltrexone (Vivitrol) 380 mg IM QM	Blurred Vision, Self-Reported Seizure, Vomiting, "Coma," pneumonia	Panic attacks, depression, alcohol dependence/ diazepam, bupropion (Wellbutrin), hydrocodone, methadone, sertraline	Hospitalized, and Improving

ISR # Source RCV Yr	Age (yr) Gender	Reported Suspect Drug	Reported Event	PMH/ Concurrent Drugs	Outcome
5486406 US 2007	49 Female	Naltrexone (Vivitrol) 380 mg IM QM	Lightheadedness, Dizziness, Nausea, Delirium, Respiratory Depression, Aggression	Hypothyroidism, hyperlipidemia, bipolar, migraines, alcoholism/ lamotrigine, lithium, quetiapine, bupropion (Wellbutrin SR), venlafaxine, levothyroxine, atorvastatin, Lyrica, sumatriptan	Hospitalized, and discharged
5660496 US 2008	48 Female	Naltrexone (Vivitrol) 380 mg IM QM	Injection Site Reaction	Alcohol dependence/ bupropion (Wellbutrin XL), quetiapine, buspirone, acamprosate,	Naloxone DC; treated with steroids and NSAIDS
5948512 ES 2008	48 Male	Bupropion 300 mg QD	Published case report of acute hepatitis (hepatomegaly of 2 cm and mucocutaneous jaundice)	---/ disulfiram, naltrexone	Bupropion DC; event resolved
6192016 FI 2009	53 Male	Bupropion (Zyban) 150 mg unknown frequency; Isoniazide unknown dose	Anxiety, Suicidal Ideation, Mood Change	Smoking, latent TB, rheumatic disease/ naltrexone, etanercept	Hospitalized; treated with mirtazapine; events continue
1932464 US 1997	23 Male	Methylphenidate SR 20 mg	Premature Ejaculation	Drug and alcohol abuse, ADHD/ bupropion (Wellbutrin), valproic acid, naltrexone (ReVia)	Unknown
3240459 US 1999	47 Female	Thioridazine 50 mg QD	Akathisia	Bipolar disorder/ naltrexone 50 mg QD, bupropion (Wellbutrin) 150 mg QD, gabapentin 400 TID, clonazepam 1 mg BID	Thioridazine DC and akathisia subsided in 48 hours

ISR # Source RCV Yr	Age (yr) Gender	Reported Suspect Drug	Reported Event	PMH/ Concurrent Drugs	Outcome
3332082 US 1999	21 Female	Venlafaxine 75 mg BID	Urine drug screen positive for PCP	Alcohol and drug addiction/ bupropion (Wellbutrin) 150 mg QD, naltrexone 50 mg QD, gabapentin 800 mg QD, trazodone 100 mg QHS	Unknown
3919300 US 2002	48 Female	Oxcarbazepine 300 mg BID and 600 mg QHS	Hyponatremia	EBV, arrhythmia, s/p TIA, asthma/ quetiapine 700 mg QD, naltrexone 25 mg BID, bupropion SR 100-200 mg QD, pantepazole 40 mg QD, atenolol 25 g QHS, inhalers	Oxcarbazepine DC; salt intake increased
4340824 US 2004	30 Female	Lithium (Eskalith) 450 mg BID	Drug Exposure During Pregnancy (7 weeks gestation)	Manic-depressive/ naltrexone, bupropion (Wellbutrin SR), zonisamide	Reporter referred to the Wellbutrin Pregnancy Registry
5756217 US 2008	55 Male	Varenicline (Chantix) 1 mg BID	Worsening Depression	---/ naltrexone, bupropion (Wellbutrin), buspirone, valproic acid 500 mg BID, lansoprazole 30 mg QD, indomethacin 50 mg BID, cyclobenzaprine 10 mg QD, terazosin 2 mg BID, inhalers	Varenicline DC; outcome unknown
6441117 US 2009	39 Female	Lisdexamfetamine (Vyvanse) 60 mg QD	"Swollen" Tongue, Mouth, and Lips; Memory Impairment, Mood Change	"---/ escitalopram 20 mg, bupropion (Wellbutrin) 300 mg, naltrexone 50 mg, trazodone 100 mg	Lisdexamfetamine DC; symptoms subsided

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200063	ORIG-1	OREXIGEN THERAPEUTICS INC	CONTRAVE® (Naltrexone HCl and Bupropion HCl)

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

/s/

JO H WYETH
08/17/2010

LANH GREEN
08/17/2010

MARK I AVIGAN
08/17/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 200063 BLA# n/a	NDA Supplement #: n/a BLA STN # n/a	Efficacy Supplement Type SE-n/a
Proprietary Name: CONTRAVE Established/Proper Name: naltrexone HCl and bupropion HCl Dosage Form: extended release tablets Strengths: 4 mg/90 mg and 8 mg/90 mg		
Applicant: Orexigen Agent for Applicant (if applicable):		
Date of Application: March 31, 2010 Date of Receipt: March 31, 2010 Date clock started after UN:		
PDUFA Goal Date: January 31, 2011		Action Goal Date (if different):
Filing Date: May 30, 2010		Date of Filing Meeting: May 24, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 4- new combination		
Proposed indication(s)/Proposed change(s): Treatment of obesity and weight management, including weight loss and maintenance of weight loss with a new combination of approved drug products.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: clinical benefit and safety (21	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

CFR 314.610/21 CFR 601.42)				
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): IND 68,858				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	×			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	×			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	×			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		×		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	×			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		×																		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			×																	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			×																	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:		×		After communicating with the sponsor, the listed products are Revia for naltrexone HCL and Wellbutrin SR for bupropion HCL.																
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		×																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>		×																		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 3 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	×																			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?			×	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) × All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	×			
Index: Does the submission contain an accurate comprehensive index?		×		Company was notified and stated the CI is the eCTD backbone.
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	×			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>	×			Consult sent on April 12, 2010.
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #				

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	×			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	×			CMC questioned if the sponsor was ready for inspection. The sponsor was notified and responded in submission 5/4/10 that they were ready for inspection.
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	×			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	×			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	×			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	×			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification	×			

<p>(that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				
--	--	--	--	--

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	×			Meeting TBD
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		×		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>		×		<p>PMHS asking for the following in the 74 day letter (b) (4)</p> <div style="background-color: #cccccc; height: 150px; width: 100%;"></div> <p>Within 30 days of the date of this letter, sponsor needs to submit a pediatric plan outlining the pediatric studies that are planned to conduct to meet the PREA requirements</p>
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>				

<u>BPCA</u> (NDAs/NDA efficacy supplements only):		×		
Is this submission a complete response to a pediatric Written Request?				
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i>				

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			Sponsor got a conditionally acceptable granted letter on 2/2/10 for "Contrace". The sponsor submitted for proprietary TN review on 5/14/10.
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	×			
Is the PI submitted in PLR format?	×			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			×	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	×			Consult sent on 6/4/10
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	×			
REMS consulted to OSE/DRISK?	×			Consult sent to OSE on 4/13/10 for MedGuide.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	×			Consult sent to OSE on 4/13/10 for MedGuide.
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label			

	<input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>				Response from meeting minutes on 5/24/06 under IND 68,858: A thorough QT study is not required. However, arrhythmic risk and the potential for QT prolongation must still be assessed for these drug combinations. Review of the original NDAs of the individual components, the AERS database, literature, postmarketing data, and careful evaluation (e.g., ECGs at Cmax) in the proposed phase 2 and 3 studies will be required to confirm that there is no increased risk for arrhythmias. You should also strongly consider evaluating the effects of your fixed-dose combinations on cardiac repolarization in preclinical tests: hERG channel assay, etc.

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): October 1, 2007 <i>If yes, distribute minutes before filing meeting</i>	×			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 14, 2009 <i>If yes, distribute minutes before filing meeting</i>	×			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		×		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 24, 2010

BLA/NDA/Supp #: 200063

PROPRIETARY NAME: Contrave

ESTABLISHED/PROPER NAME: naltrexone HCL/ bupropion HCL extended release tablets

DOSAGE FORM/STRENGTH: 4 mg/90 mg and 8 mg/90 mg

APPLICANT: Orexigen Therapeutics, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): This is a new combination of approved drugs for weight loss and management.

BACKGROUND: This a new 505(b)(2) combination for fixed dose products: Contrave [naltrexone HCL and bupropion extended release tablets] (4 mg/90 mg and 8 mg/90 mg) for the treatment of obesity and weight management, including weight loss and maintenance of weight loss. The sponsor claims both products interact in the central nervous system to decrease food intake and increase energy expenditure, resulting in synergistic and sustainable weight loss.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Meghna Jairath Pat Madara	Y
	CPMS/TL:	Enid Galliers Leah Ripper	Y
Cross-Discipline Team Leader (CDTL)	Eric Colman, MD		Y
Clinical	Reviewer:	Eileen Craig, MD	Y
	TL:	Eric Colman, MD	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Manoj Khurana, PhD	Y
	TL:	Sally Choe, PhD	Y
Biostatistics (DOB7- Safety)	Reviewer:	Xiao Ding, PhD	Y
	TL:	Mat Soukup (TL), PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Patricia Brundage, PhD	Y
	TL:	Todd Bourcier, PhD	Y
Statistics (Efficacy)	Reviewer:	Janice Derr, PhD	Y
	TL:	Todd Sahlroot, PhD	Y
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Xavier Ysern, PhD; Tapash Gosh (Biopharm), PhD	Y
	TL:	Su Tran	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	n/a	
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	n/a	
	TL:		
Facility Review/Inspection (DSI)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Rick Abate	N
	TL:		
OSE/DRISK (REMS)	Reviewer:	Shawana Hutchins	N
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon, PharmD	N

	TL:	Tejashri Purohit-Sheth, MD	N

Other reviewers : all the listed reviewers attended	CSS: Chad Reissig (reviewer), PhD & Lori Love (TL), PhD PMHS: Mildred Wright (RPM) & Beth Durmowicz, MD (MO) OSE: Margarita Tossa (RPM) Safety: Amy Egan, MD (Deputy Dir Safety) & John Bishai, PhD (RPM) OCP: Dionna Green	Y
Other attendees	Janice Weiner-Office of Regulatory Policy	N

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? 	<input checked="" type="checkbox"/> YES Date if known:

<p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p><input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<p>Comments:</p>	
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p>× Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable × FILE <input type="checkbox"/> REFUSE TO FILE</p> <p>× Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>× YES NO</p> <p>YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p>× Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>× YES <input type="checkbox"/> NO</p> <p>× YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p>× Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Eric Colman, MD</p> <p>21st Century Review Milestones (see attached) (optional):</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p>×</p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p>× Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p>× Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p>ACTIONS ITEMS</p>	
<p><input type="checkbox"/></p>	<p>Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>
<p><input type="checkbox"/></p>	<p>BLA/BLA supplements: If filed, send 60-day filing letter</p>

<input type="checkbox"/>	
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none">• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)• notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200063

ORIG-1

OREXIGEN
THERAPEUTICS
INC

CONTRAVE® (Naltrexone HCl
and Bupropion HCl)

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/s/

MEGHNA M JAIRATH
06/10/2010

**REGULATORY PROJECT MANAGER LABELING REVIEW
(PHYSICIAN LABELING RULE)**

Division of Division of Metabolism and Endocrinology Products

Application Number: NDA 200063

Name of Drug: Contrave (naltrexone HCl/bupropion HCl)

Applicant: Orexigen Therapeutics, Inc.

Material Reviewed:

Submission Date(s): March 31, 2010 (original SPL submitted) and May 4, 2010 (word version updated)

Receipt Date(s): March 31, 2010 and May 4, 2010

Submission Date of Structure Product Labeling (SPL): March 31, 2010 and May 4, 2004

Type of Labeling Reviewed: WORD/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

1. Under Highlights Overview Section:

- Add spaces between each major heading. (appears in WORD version only).
- ~~Delete~~ and Add: See 17 for PATIENT COUNSELING INFORMATION and (b) (4)
[REDACTED] Medication Guide. (appears in WORD version only).

2. Under Full Prescribing Information Table of Contents:

- The same title for the boxed warning that appears in the Highlights and Full Prescribing Information must also appear at the beginning of the Table of Contents in upper-case letters and bold type: Add, Warning: **Suicidality and Antidepressant Drugs**. (not added in both SPL and WORD versions).
- Delete all periods after the numbers of the section and subsection headings. (appears in SPL version only)
- Under section 17 Patient counseling Information:
 - ~~Delete~~ and Add: 17.1 (b) (4) Physician Instructions. (appears in both SPL and WORD versions)
 - (b) (4)
(appears in both SPL and WORD versions)

3. Under Full Prescribing Information

- Delete all periods after the numbers of the section and subsection headings. (appears in both SPL and WORD versions).
- Some subheadings in WORD version are not bolded. Bold all subheadings.
- Under 17 Patient Counseling Information:
 - ~~Delete~~ and Add: “Patient information is printed at the end of this insert. To assure safe and effective use of CONTRAVE, this information and instructions provided in the (b) (4) Medication Guide should be discussed with patients.” (appears in both SPL and WORD versions)
 - ~~Delete~~ and Add: 17.1 (b) (4) Physician Instructions. (appears in both SPL and WORD versions)
 - ~~Delete~~ : (b) (4) (appears in both SPL and WORD versions)
- (b) (4) (appears in both SPL and WORD versions)

Recommendations

Please address the identified deficiencies/issues and re-submit labeling by August 16, 2010. This updated version of labeling will be used for further labeling discussions.

Meghna M. Jairath, Pharm.D.
REGULATORY PROJECT MANAGER

Supervisory Comment/Concurrence:

Enid Galliers,
Chief, Project Management Staff

Drafted: MMJ/06.07.10

Revised/Initialed:

Finalized:

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200063

ORIG-1

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CONTRAVE® (Naltrexone HCl
and Bupropion HCl)

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/s/

MEGHNA M JAIRATH
06/10/2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200063

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and Bupropion HCl)

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/s/

MEGHNA M JAIRATH
04/28/2010