

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number: 200063
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Product: CONTRAVE® (naltrexone HCl and bupropion HCl)
Extended-Release Tablets
Indication: Treatment of obesity and weight management
Applicant: Orexigen Therapeutics Inc.
Review Division: Division of Metabolism and Endocrinology Products
(HFD-510)
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1 Executive Summary

1.1 Introduction

This is a 505(b)(2) application for an extended release fixed dose combination (FDC) drug product of naltrexone HCl and bupropion HCl for the treatment of obesity and weight management. Orexigen Therapeutics Inc. did not conduct a nonclinical development/animal toxicology program. This 505(b)(2) application relies primarily on the Agency findings of the safety and efficacy as reflected in the approved product labels for ReVia® (naltrexone HCl) and Wellbutrin SR® (bupropion HCl). The rights of reference for the nonclinical data in either NDA 18-932 for ReVia® (naltrexone HCl) or NDA 20-358 for Wellbutrin SR® (bupropion HCl) were not obtained.

The initial Pharmacology/Toxicology NDA Review and Evaluation completed in December 2010 concluded that the pharmacology and toxicology data supported the approval of CONTRAVE for the proposed obesity indication. However, a Complete Response Letter (CRL) was issued in January 2011 requesting the 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. No nonclinical issues were cited in the CRL.

On 10 December 2013, the sponsor submitted a complete response to address the approval deficiency noted in the CRL.

1.2 Brief Discussion of Nonclinical Findings

This review addresses the proposed labeling for CONTRAVE, as well as the proposed juvenile toxicology study to support the deferred pediatric studies. Refer to the initial Pharmacology/Toxicology NDA Review and Evaluation (December 2010) for the full review of the pharmacology and toxicology data to support the approval of the proposed obesity indication in adults.

The recommended CONTRAVE labeling changes include changes to the established pharmaceutical class and safety margins. The pharmacological class selected by the sponsor was dual pro-opiomelanocortin cell (POMC) enhancer. However, as the exact neurochemical weight loss effects of CONTRAVE are not fully understood, the use the established pharmaceutical classes in the referenced labels for naltrexone and bupropion are considered more clinically meaningful and scientifically valid. The safety margins were corrected using a 100 kg body weight, which is appropriate for an obese population. The Division concurs with the selection of Pregnancy Category X for CONTRAVE as weight loss is contraindicated during pregnancy based on clinical considerations and is consistent with the other weight loss drugs.

The sponsor also provided an outline for a juvenile animal study in rats to support the deferred pediatric safety and efficacy studies in children with obesity ages 12 to 17 years (inclusive) and ages 7 to 11 years (inclusive). 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, and 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, also has pharmacological activity and therefore has the potential to cause behavior, learning, and memory changes in pre-pubertal/pubertal animals and humans. The effects of

naltrexone, bupropion, and hydroxybupropion on learning/memory/behavioral development should be assessed in juvenile animals prior to initiating the pediatric safety and efficacy 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.

1.3 Recommendations

1.3.1 Approvability

AP (Approval)

1.3.2 Additional Nonclinical Recommendations

Naltrexone and bupropion, as well as hydroxybupropion, the major active metabolite of bupropion in humans, possess CNS activity with the potential to cause adverse outcomes or irreversible effects on learning, memory, and behavioral development as a result of exposure during the pre-pubertal/pubertal period. As a post marketing requirement (PMR), a juvenile animal study with the combination of bupropion and naltrexone to assess behavior/motor activity, learning and memory, growth, sexual maturation, and mating/fertility is required prior to initiating the pediatric safety and efficacy studies in children. The study design should incorporate assessment of reversibility after a drug-free period, and toxicokinetic exposure. The study should also include the evaluation of the CNS active major human metabolite hydroxybupropion. As metabolism of bupropion in mice appears to be more similar to humans regarding exposure to hydroxybupropion than rats, the mouse appears to be the more suitable species for evaluation.

1.3.3 Labeling

For this 505(b)(2) application for which the sponsor did not conduct a nonclinical development/animal toxicology program, the language used in the label should reflect the referenced drug labels of ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl).

Safety margins in the proposed label were estimated using body surface area exposure (mg/m²) based on the body weight of ^{(b) (4)} kg. The safety margins have been corrected using a 100 kg body weight, which is appropriate for an obese population.

The pharmacological class proposed by the sponsor is dual pro-opiomelanocortin cell (POMC) enhancer. As the pharmaceutical class should be clinically meaningful and scientifically valid (i.e., not theoretical), it is more appropriate to use the established pharmaceutical classes in the referenced labels for each drug product given that the exact mechanism of action for the weight loss effects of FDC drug product are not fully established.

Pregnancy Category 'C' was recommended for the FDC drug product in the previous review given that both naltrexone and bupropion are labeled as Pregnancy Category 'C.' However, Pregnancy Category 'X' is now recommended for the FDC drug product as it is contraindicated during pregnancy based on clinical considerations of weight loss in pregnant women. This is consistent with other obesity drugs.

Changes/additions to the proposed label are underlined.

INDICATIONS AND USAGE

CONTRAVE is a combination of naltrexone, an opioid antagonist, and bupropion, an aminoketone antidepressant, (b) (4) indicated (b) (4) with (b) (4) an initial body mass index (BMI) of:

1 INDICATIONS AND USAGE

CONTRAVE®, (b) (4)

8 USE IN SPECIFIC POPULATIONS, 8.1 Pregnancy

Pregnancy Category X.

Risk Summary

CONTRAVE is contraindicated during pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard of maternal weight loss to the fetus.

Animal Data

Reproduction and developmental studies have not been conducted for the combined products naltrexone and bupropion in CONTRAVE.

Separate studies with bupropion and naltrexone have been conducted in pregnant rats and rabbits.

Naltrexone administered orally has been shown to increase the incidence of early fetal loss in rats administered ≥ 30 mg/kg/day (180 mg/m²/day) and rabbits administered ≥ 60 mg/kg/day (720 mg/m²/day), doses at least (b) (4) 5 and (b) (4) 60 times, respectively, the maximum recommended human dose [MRHD] of the naltrexone component in CONTRAVE on a mg/m² basis. There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 200 mg/kg/day (approximately 100 and 200 times the recommended therapeutic dose, respectively, based on body surface area). Rats do not form appreciable quantities of the major human metabolite, 6-β-naltrexol; therefore, the potential reproductive toxicity of the metabolite in rats is not known.

Bupropion was administered orally in studies conducted in rats and rabbits at doses up to 450 and 150 mg/kg/day, respectively (approximately (b) (4) 20 and (b) (4) 15 times the MRHD, respectively, of the bupropion component in CONTRAVE on a mg/m² basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately (b) (4) 2 times the MRHD on a mg/m² basis) and greater. Decreased fetal weights were seen at 50 mg/kg and greater (approximately 5 times the MRHD on a mg/m² basis). When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately (b) (4) 15 times the MRHD of the bupropion component in CONTRAVE on a mg/m² basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

11 DESCRIPTION

CONTRAVE (b) (4) containing naltrexone hydrochloride and bupropion hydrochloride.

Naltrexone hydrochloride, USP, an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. Naltrexone hydrochloride is also related to the potent opioid antagonist, naloxone, or n-allylnoroxymorphone. Naltrexone hydrochloride has the chemical name of morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, hydrochloride, (5 α). The empirical formula is C₂₀H₂₃NO₄•HCl and the molecular weight is 377.86. The structural formula is:

Bupropion hydrochloride is an antidepressant of the aminoketone class. Bupropion hydrochloride closely resembles the structure of diethylpropion. It is designated as (\pm)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino -]-1-propanone hydrochloride. It is related to phenylethylamines. The empirical formula is C₁₃H₁₈ClNO•HCl and molecular weight is 276.2. The structural formula is:

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact neurochemical (b) (4) effects of CONTRAVE are not fully understood. CONTRAVE has two components: naltrexone, an (b) (4) opioid antagonist, and bupropion, a relatively weak inhibitor of the neuronal reuptake of dopamine and norepinephrine (b) (4)

(b) (4)

12.2 Pharmacodynamics

(b) (4)
Combined, bupropion and naltrexone increases the firing rate of (b) (4) hypothalamic pro-opiomelanocortin (POMC) neurons in vitro.

13 NONCLINICAL TOXICOLOGY STUDIES

13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility

Studies to evaluate carcinogenesis, mutagenesis, or impairment of fertility with the combined products in CONTRAVE have not been conducted. The following findings are from studies performed individually with naltrexone and bupropion. The potential carcinogenic, mutagenic and fertility effects of the metabolite 6-β-naltrexol are unknown.

In a two-year carcinogenicity study in rats with naltrexone, there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females. The incidence of mesothelioma in males given naltrexone at a dietary dose of 100 mg/kg/day (approximately 50^{(b) (4)} times the recommended therapeutic dose on a mg/m² basis for the naltrexone maintenance dose for CONTRAVE) was 6%, compared with a maximum historical incidence of 4%. The incidence of vascular tumors in males and females given dietary doses of 100 mg/kg/day was 4%, but only the incidence in females was increased compared with a maximum historical control incidence of 2%. There was no evidence of carcinogenicity in a two-year dietary study with naltrexone in male and female mice.

Lifetime carcinogenicity studies of bupropion were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately 15^{(b) (4)} and 3^{(b) (4)} times the maximum recommended human dose (MRHD) of the bupropion component in CONTRAVE, respectively, on a mg/m² basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 5^{(b) (4)} to 15^{(b) (4)} times the MRHD of the bupropion component in CONTRAVE on a mg/m² basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

There was limited evidence of a weak genotoxic effect of naltrexone in one gene mutation assay in a mammalian cell line, in the *Drosophila* recessive lethal assay, and in non-specific DNA repair tests with *E. coli*. However, no evidence of genotoxic potential was observed in a range of other *in vitro* tests, including assays for gene mutation in bacteria, yeast, or in a second mammalian cell line, a chromosomal aberration assay, and an assay for DNA damage in human cells. Naltrexone did not exhibit clastogenicity in an *in vivo* mouse micronucleus assay.

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1 of 3 *in vivo* rat bone marrow cytogenetic studies.

^{(b) (4)}—Naltrexone administered orally to rats caused a significant increase in pseudopregnancy and a decrease in pregnancy rates ^{(b) (4)} in rats 100 mg/kg/day (approximately 50^{(b) (4)} times the MRHD of the naltrexone component in CONTRAVE on a mg/m² basis). There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.

A fertility study of bupropion in rats at doses up to 300 mg/kg/day (approximately 15 times the MRHD of the bupropion component in CONTRAVE on a mg/m² basis) revealed no evidence of impaired fertility.

2 Drug Information

2.1 Drug

CAS Registry Number

Naltrexone HCl: 16676-29-2

Bupropion HCl: 31677-93-7

Code Name

Naltrexone HCl: (b) (4) (b) (4) (b) (4)

Bupropion HCl: (b) (4) (b) (4) (b) (4)

Chemical Name

Naltrexone HCl:

- Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy, hydrochloride, (5 α)- (USAN 1)
- 17-(Cyclopropylmethyl)-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one, hydrochloride (USAN 2, IUPAC)

Bupropion HCl:

- 1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (1:1) (USAN 1)
- (2*RS*)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino] propan-1-one hydrochloride (USAN 2)
- (\pm)-2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one hydrochloride (IUPAC)
- (\pm)-2-(tert-butylamino)-3'-chloropropiophenone hydrochloride

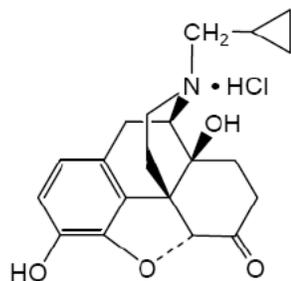
Molecular Formula/Molecular Weight

Naltrexone HCl: C₂₀H₂₃NO₄ • HCl (C₂₀H₂₄ClNO₄)/377.86

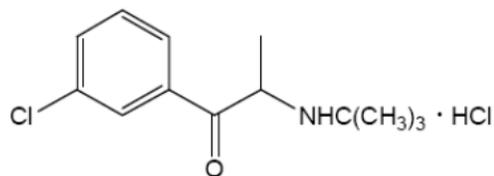
Bupropion HCl: C₁₃H₁₈ClNO • HCl (C₁₃H₁₉Cl₂NO)/276.2

Structure or Biochemical Description

Naltrexone HCl:



Bupropion HCl:



Pharmacologic Class

Naltrexone is an opioid antagonist.

Bupropion is an aminoketone antidepressant.

2.2 Relevant NDAs and DMFs

NDA 18-932 (ReVia[®], naltrexone HCl)

NDA 20-358 (Wellbutrin SR[®]; bupropion HCl)

- DMF (b) (4) Type II; (b) (4) naltrexone HCl)
- DMF (b) (4) (Type II; (b) (4) naltrexone HCl)
- DMF (b) (4) (Type II, (b) (4) bupropion HCl)
- DMF (b) (4) (Type II (b) (4) bupropion HCl)

2.3 Drug Formulation

The FDC drug product (naltrexone HCl 4 or 8 mg and bupropion HCl 90 mg) is a combination drug product formulated as a film coated trilayer tablet for (b) (4) release oral delivery; (b) (4)

Both active pharmaceutical ingredients (bupropion HCl and naltrexone HCl) conform to the requirements of the respective current USP monographs. Two drug product strengths, which (b) (4)

Drug Product Unit Composition (8 mg/tablet Naltrexone HCl Presentation)

Ingredient	Amount			Function
	mg/ tablet	wt% of layer	wt% of tablet ¹	
(b) (4)				
Bupropion Hydrochloride USP	90.0		(b) (4)	Active ingredient
L-Cysteine Hydrochloride USP	(b) (4)			(b) (4)
Microcrystalline Cellulose (b) (4) NF				
Hydroxypropyl Cellulose (b) (4) NF				
Magnesium Stearate NF				
(b) (4)				
Microcrystalline Cellulose (b) (4) NF	(b) (4)			(b) (4)
Lactose Anhydrous NF				
Crospovidone (b) (4) NF				
Magnesium Stearate NF				
FD&C Blue #2 Aluminum Lake				
(b) (4)				
Naltrexone Hydrochloride (b) (4) USP	8.0			Active ingredient
Microcrystalline Cellulose (b) (4) NF	(b) (4)			(b) (4)
Hypromellose USP (b) (4)				
Hydroxypropyl Cellulose (b) (4) NF				
Edetate Disodium USP				
Colloidal Silicon Dioxide NF (b) (4)				
Lactose Monohydrate (b) (4) NF				
Magnesium Stearate NF (b) (4)				
(b) (4)				
Opadry II Blue (b) (4)				(b) (4)
Overall total:	680		100	(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product. Each compendial excipient to be used in the proposed commercial drug product meets the requirements of the respective current USP or NF monograph.

2.5 Comments on Impurities/Degradants of Concern

No safety concerns from drug substance impurities/degradants were identified.

Degradants

All known drug product degradants are characterized compounds, and are specified at or below the ICH Q3B(R2) qualification threshold and/or have been qualified at levels well above the specified limits from data in Wellbutrin SR[®] NDA 20-358 for which right of reference was obtained.

Impurities

Naltrexone

With the exception of (b) (4) a limit of NMT (b) (4) % has been established for individual specified impurities and NMT (b) (4) % for any unspecified impurity based on the maximum daily clinical dose of naltrexone (32 mg/day), which meets the ICH Q3A(R2) drug substance impurity qualification threshold. The impurity

Proposed Acceptance Criteria of Bupropion Impurities (Sponsor's Table)

(b) (4)	NMT	(b) (4) %	Current USP monograph
	NMT	%	
NMT	(b) (4) ppm	(b) (4) %	Type II DMF Method/ (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The FDC drug product of naltrexone HCl and bupropion HCl is indicated as an adjunct to reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial mass index $\geq 30 \text{ kg/m}^2$ or $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight-related co-morbidity.

The recommended daily dose is two extended release tablets of naltrexone HCl 8 mg/bupropion HCl 90 mg (8/90) administered twice daily for a total dose of 32 mg naltrexone and 360 mg bupropion. Dosing is escalated over a 3-week period until achieving the total daily maintenance dose. Treatment initiation and escalation with naltrexone HCl 4 mg/bupropion HCl 90 mg (4/90) SR tablets may be considered.

2.7 Regulatory Background

As an oral monotherapy, naltrexone HCl was approved in 1984 for the treatment of opioid addiction and for alcohol dependence in 1995. In 2006, an injectable, extended-release formulation of naltrexone was approved for alcohol dependence. Of the approved naltrexone drug products, ReVia[®] (50 mg naltrexone HCl tablet) was selected as the listed drug as it was determined to be the closest to that in the FDC drug product of naltrexone HCl/bupropion HCl with respect to dosage strength and route of administration.

Bupropion HCl was first approved as an antidepressant in 1985 (Wellbutrin[®]). Sustained-release formulations were approved in 1996 (Wellbutrin SR[®]; twice daily dosing) and 2003 (Wellbutrin XL[®]; once daily dosing). In 1997, a controlled-release formulation of bupropion HCl was approved as an aid to smoking cessation (Zyban[®]). A hydrobromide salt of bupropion (Aplenzin[™]) was also approved for the treatment of depression. Wellbutrin SR[®] (bupropion HCl) was selected as the most appropriate listed drug for this application as it was determined to be the closest with respect to dosage strength and route of administration. The usual adult target dose for Wellbutrin SR[®] is 300 mg/day, administered as 150 mg twice daily. An increase in dosage to the maximum of 400 mg/day, given as 200 mg twice daily, may be considered after several weeks of treatment at 300 mg/day.

In March 2010, Orexigen submitted a New Drug Application (NDA) for CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) Extended Release tablets pursuant to section 505(b)(2). In January 2011, the Division issued a Complete Response Letter (CRL) outlining the approval deficiency requiring the sponsor to conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events (MACE) in overweight and obese subjects treated with CONTRAVE. There were no nonclinical issues cited in the CRL.

3 Studies Submitted

3.1 Studies Reviewed

None.

3.3 Previous Reviews Referenced

NDA 200063 Pharmacology/Toxicology NDA Review and Evaluation (December 2010).

4 Pharmacology

In support of this 505(b)(2) new drug application, one safety pharmacology study was conducted to assess the effects of naltrexone and 6- β -naltrexol on the rapidly activating inward rectifying potassium current (I_{Kr}) conducted by hERG channels. No other nonclinical pharmacology studies were conducted for this 505(b)(2) submission. The review relied upon information from the approved labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl), as well as information from the published literature.

It is hypothesized that the two drugs have synergistic actions in the hypothalamus and the mesolimbic DA circuit (reward system) to cause weight loss. Bupropion is thought to stimulate the release of α -MSH from pro-opiomelanocortin (POMC) neurons in the arcuate nucleus in the hypothalamus, which leads to downstream effects on feeding behavior (i.e., decreased food consumption). Whereas naltrexone is thought to block the inhibitory feedback loop mediated by β -endorphin at mu opioid receptors on POMC neurons to facilitate a more potent and longer-lasting activation of POMC neurons. Bupropion and naltrexone may also act synergistically via the ventral tegmental nucleus (VTA) in the mesolimbic system. Dopamine and endogenous opioid peptides are key neurotransmitters influencing the activity of this pathway. Direct injection of naltrexone and bupropion into the VTA in mice produced a synergistic reduction in food intake demonstrating that naltrexone and bupropion have independent and complementary actions in the appetite regulatory center and the reward system.

5 Pharmacokinetics/ADME/Toxicokinetics

No new nonclinical pharmacokinetic/ADME/toxicokinetic studies were conducted for this 505(b)(2) submission. The nonclinical ADME properties and pharmacokinetics (PK) of naltrexone and bupropion, individually, were previously established. The ADME properties of naltrexone and bupropion are provided in the labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl), as well as in the published literature.

In lieu of nonclinical PK studies, clinical studies in the Phase 1 clinical program established the single-dose (two 8 mg naltrexone HCl/90 mg bupropion HCl tablets) and multiple-dose (two 8 mg naltrexone HCl/90 mg bupropion HCl tablets; twice daily for 1 week) PK profiles of naltrexone/bupropion tablets. These studies also collected ADME data on the main metabolites of naltrexone (6 β -naltrexol) and bupropion (hydroxybupropion, erythrohydrobupropion, and threoxyhydrobupropion).

6 General Toxicology

No new general toxicology studies were conducted for this 505(b)(2) submission. There have been no nonclinical studies conducted with the combination of naltrexone HCl and bupropion HCl. The approved label for Wellbutrin SR[®] (bupropion HCl), as well as the published literature provided information regarding the target organs of toxicity of naltrexone

and bupropion. No-effect dosage levels with adequate margins of safety were identified for each of the adverse treatment-related changes observed with naltrexone. For bupropion, treatment-related, reversible hepatic adverse findings were noted in both the rat and dog at doses that are clinically relevant (mg/m² basis; as low as ~1X MRHD of 360 mg bupropion). The general toxicological profile of naltrexone and bupropion supported the currently approved clinical indications. The known pressor effect of bupropion, which is evident from studies in animals and humans, may contribute more prominently to the risk/benefit profile for the intended obese population which is already at an increased long-term cardiovascular risk compared to the currently approved clinical indications.

7 Genetic Toxicology

No new genetic toxicology studies were conducted for this 505(b)(2) submission. The genotoxicity of naltrexone and bupropion, separately, were previously established in *in vitro* and *in vivo* genotoxicity studies. Summaries of the genotoxicity findings are provided in the labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl).

8 Carcinogenicity

No new carcinogenicity studies were conducted for this 505(b)(2) submission. The carcinogenicity of naltrexone and bupropion, individually, were each previously established in two rodent species (mouse and rat) as established in the labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl). Only naltrexone in the rat was associated with neoplastic findings (i.e., testicular mesotheliomas and tumors of vascular origin) for which a NOEL was established. The carcinogenicity profile of naltrexone and bupropion supported the currently approved clinical indications and does not raise special concern for the intended obese population.

9 Reproductive and Developmental Toxicology

No new reproductive toxicology studies were conducted for this 505(b)(2) submission. The developmental and reproductive toxicity of naltrexone and bupropion, separately, were previously established. The findings of these studies are provided in the labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl). Bupropion and naltrexone are classified in Pregnancy Category C. However, Pregnancy Category X is recommended for the FDC drug product as it is contraindicated during pregnancy based on clinical considerations of weight loss in pregnant women, which is consistent with the previously approved obesity drugs.

Juvenile Development

The sponsor submitted a pediatric plan that outlines a rat juvenile toxicology study for the combination of naltrexone and bupropion to support the proposed pediatric clinical trials in ≥ 7 to ≤ 17 year old children with obesity. Neither naltrexone nor bupropion have been evaluated in juvenile animal or clinical pediatric studies.

Proposed Juvenile Rat Study

Prior to the initiation of the Phase 3 pediatric studies, the sponsor plans to conduct a rat juvenile toxicology study to obtain toxicity and toxicokinetic data on the potential adverse effects of combination dosing with naltrexone and bupropion on postnatal growth and development.

(b) (4)



The EMA's Pediatric Committee (PDCO) has required the juvenile animal studies be conducted in prepubertal/pubertal mice to support pediatric development for the product in the EU (August 2013). Despite arguments from the sponsor that it would be difficult to obtain toxicokinetic data in a standardized fashion and that long-term dosing by oral gavage in juvenile mice would be extremely difficult, the PDCO maintained its position as mice are considered the best model of human pharmacokinetics. The sponsor agreed with the caveat that if feasibility studies indicated mice would not be appropriate, a request to amend the PIP to conduct the studies in a more suitable species (e.g., rats) would be submitted. As of April 2014, no feasibility studies have been conducted by the sponsor.

The major metabolite of bupropion, hydroxybupropion, has been found to play a significant role in the anti-depressant activity of bupropion (Martin et al., 1990), as well as its convulsive liability (Silverstone et al., 2008). Therefore, like bupropion, it has the potential to cause behavior, learning, and memory changes in pre-pubertal/pubertal animals and humans.

The plasma concentration of this major pharmacologically active metabolite hydroxybupropion exceeds that of bupropion in humans after single and multiple doses twice daily of naltrexone HCl 8 mg/bupropion HCl 90 mg (Study NB-236) with a mean AUC metabolite to parent ratio of 12-17. Due to apparent differences in drug metabolism between species, the plasma concentration of hydroxybupropion in the rat is relatively low compared to that of bupropion following single and multiple doses (Welch et al., 1987). However, relatively high concentrations of hydroxybupropion were found in mouse plasma suggesting that the mouse is a more appropriate model of human pharmacokinetics (refer to table below). In humans, concentrations of hydroxybupropion in the cerebral spinal fluid also exceeded those of bupropion with hydroxybupropion concentrations approximately 6 times greater than those of bupropion (Golden et al., 1988). Hydroxybupropion also appears to be the predominant compound in the mouse brain with levels approximately 3 times higher than bupropion; the concentration of hydroxybupropion compared to that of bupropion was relatively low in the rat

brain. Therefore, the mouse appears to be the more suitable species for evaluating the potential effects of bupropion and its major pharmacologically active metabolite.

Plasma Concentrations of Bupropion and Hydroxybupropion in the Rat and Mouse (Welch et al., 1987)					
Species (Bupropion Dose)	Drug/Metabolite	First Day		14 Daily Doses	
		AUC (ng·h/mL)	t_{1/2} (h)	AUC (ng·h/mL)	t_{1/2} (h)
Rat (200 mg/kg)	Bupropion	7614	1.6	442	0.8
	Hydroxybupropion	2211	1.1	760	1
Mouse (150 mg/kg)	Bupropion	4815	1.8	489	.28
	Hydroxybupropion	13081	1.5	10055	1.49

11 Integrated Summary and Safety Evaluation

This is a 505(b)(2) application for an extended release fixed dose combination (FDC) drug product of naltrexone HCl and bupropion HCl for the treatment of obesity and weight management. This 505(b)(2) application relies primarily on the Agency findings of the safety and efficacy as reflected in the approved product labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl), which are both approved for chronic use. This review is limited to labeling changes and the proposed juvenile animal study to support the proposed pediatric studies.

To support the proposed pediatric studies, the sponsor is proposing a juvenile animal study in rats. 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 prior to initiating pediatric safety and efficacy studies. Neither drug has been evaluated in juvenile animal studies.

The endpoints to be addressed in the juvenile animal study include standard clinical pathology and toxicity endpoints, motor activity, learning and memory, growth, long bone growth, sexual maturation, and mating and fertility. The study design will also incorporate assessment of reversibility after a drug-free period, and toxicokinetic exposure.

The study will also need to evaluate the CNS-active major human metabolite of bupropion, hydroxybupropion. The EMA's Pediatric Committee (PDCO) has required the juvenile animal study use prepubertal/pubertal mice, not rats, given the bupropion metabolism differences between species. Concentrations of the hydroxybupropion in the plasma and central nervous system of the mouse are most similar to that of the human with hydroxybupropion levels exceeding those of the parent drug. In the rat, hydroxybupropion does not exceed parent drug exposure in the plasma or brain. Thus, the mouse appears to be the more suitable species.

The sponsor is planning to conduct studies to determine the feasibility of long-term dosing by oral gavage in juvenile mice, as well as obtaining toxicokinetic data in a standardized fashion. If the feasibility studies indicate mice would not be appropriate to use in the juvenile animal study, they plan to submit a request to amend the pediatric investigation plan (PIP) to conduct the juvenile study in a more suitable species (e.g., the rat). The Division will work with the PDCO to align the juvenile animal protocol to avoid conducting multiple juvenile studies in different species.

12 References

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Martin P, Massol J, Colin JN, Lacomblez L, Puech AJ. Antidepressant profile of bupropion and three metabolites in mice. *Pharmacopsychiatry*. 1990 Jul; 23(4): 187-94..

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Welch RM, Lai AA, Schroeder DH. Pharmacological significance of the species differences in bupropion metabolism. *Xenobiotica*. 1987 Mar; 17(3): 287-98.

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/s/

PATRICIA M BRUNDAGE
05/20/2014

TODD M BOURCIER
05/21/2014
P/T supports AP



**Pharmacology/Toxicology
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Products**

NDA SECONDARY REVIEW

Date:	14 Dec 2010
NDA #	200,063
Sponsor:	Orexigen Therapeutics
Drug:	Contrave naltrexone HCl and bupropion HCl FDC
Primary Reviewer:	Patricia Brundage, Ph.D.
Secondary Reviewer:	Todd Bourcier, Ph.D.

Orexigen is seeking marketing approval for Contrave, a fixed-dose combination product of naltrexone HCl and bupropion HCl, as a treatment for obesity and weight management. Dosages are escalated over the course of 4 weeks to a maximum ‘maintenance dose’ of four tablets taken daily (two in the morning and two in the evening). Each tablet contains 8mg naltrexone and 90mg bupropion, for a maximum total daily intake of 32mg naltrexone and 360mg bupropion. As a dopamine/noradrenergic sympathomimetic agent, bupropion is thought to stimulate anorexigenic proopiomelanocortin (POMC) neurons in the hypothalamus to increase satiety and reduce caloric intake, in addition to its known anti-depressant pharmacological activity. As a mu-opioid receptor antagonist, naltrexone is thought to interrupt negative feedback of opioids on POMC neurons, thereby potentiating anorexigenic activity, and to interrupt positive feedback in the mesolimbic system associated with feeding behavior. Together, the two drugs are thought to act synergistically to increase satiety, reduce caloric intake, and lessen positive reinforcement associated with excessive caloric intake.

Orexigen is seeking approval of Contrave under a 505(b)(2) regulatory pathway. Bupropion and naltrexone are approved medicines and are indicated for chronic-use conditions (depression and substance abuse, respectively). Because the treatment of obesity is also regarded as a chronic-use indication, the nonclinical information that supported the FDA’s finding of safety and efficacy for the referenced drugs (Revia and Wellbutrin) is applicable to the current application.

Dr. Brundage, the primary nonclinical reviewer, concludes that the pharmacology and toxicology data support approval of Contrave for the proposed obesity indication. No additional nonclinical studies are recommended. I concur with Dr. Brundage’s assessment.

A bridge to the nonclinical data for the referenced drugs was provided by identification and characterization of the naltrexone and bupropion drug substances present in Contrave. The content of impurities and degradants did not meet a threshold that required qualification by

additional studies, according to current ICH-Q guidances. The specification of potentially genotoxic impurities present in naltrexone and bupropion were lowered to the threshold of toxicological concern ($\leq 1.5\mu\text{g}/\text{day}$). Note that these genotoxic impurities are not unique to Contrave but are also present in the marketed referenced drugs. Genotoxicity and carcinogenicity information for the referenced drugs adequately qualified these impurities as well as the active drug substances, and is conveyed in the current labels of the referenced drugs.

The labels for the referenced drugs and the public literature report that the primary safety concerns with the use of bupropion in human subjects are also observed in animals. For example, bupropion exhibits a pressor response including increased pulmonary pressure in dogs, exerts adverse effects on the liver at high doses in rats and dogs, and elicits seizure activity in mice and dogs at low multiples of clinical exposure. Of particular interest, the increase in pulmonary pressure in dogs administered bupropion exceeds the pressor response as measured by systolic and mean blood pressure. Orexigen also provided a new study documenting that naltrexone and 6-beta naltrexol does not inhibit hERG activity and is therefore a low risk for QT prolongation. There is no evident overlap in pharmacology that would predict a diminution or exacerbation of the safety concerns with bupropion by concomitant treatment with naltrexone.

The genotoxicity, carcinogenicity, and reproductive toxicology information in the labels of the referenced drugs adequately support their use in combination for an obesity indication. Labeling for Contrave will reflect the labeling in the referenced products with safety margins recalculated to account for the daily intake of each component in the combination drug product and adjusted for the higher body mass of the intended clinical population.

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/s/

TODD M BOURCIER

12/20/2010

Nonclinical recommends AP

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number: 200063
Supporting Document/s: SDN 1, 12, and 17
Applicant's Letter Date: 31 March 2010
CDER Stamp Date: 31 March 2010
Product: CONTRAVE® (naltrexone HCl and bupropion HCl)
Extended-Release Tablets
Indication: Treatment of obesity and weight management
Applicant: Orexigen Therapeutics Inc.
Review Division: Division of Metabolism and Endocrinology Products
(HFD-510)
Reviewer: Patricia Brundage, Ph.D.
Supervisor/Team Leader: Todd Bourcier, Ph.D.
Division Director: Mary Parks, M.D.
Project Manager: Meghna Jairath

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 200063 are owned by Orexigen Therapeutics or are data for which Orexigen Therapeutics has obtained a written right of reference. Any information or data necessary for approval of NDA 200063 that Orexigen Therapeutics does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Orexigen Therapeutics does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 200063.

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1 Executive Summary

1.1 Introduction

This is a 505(b)(2) application for an extended release fixed dose combination (FDC) drug product of naltrexone HCl and bupropion HCl for the treatment of obesity and weight management. Naltrexone is a potent mu opioid antagonist, and bupropion is a biogenic amine reuptake inhibitor, mainly of dopamine (DA) and norepinephrine (NE). It is hypothesized that the two drugs have synergistic actions in the hypothalamus and the mesolimbic DA circuit (reward system) to cause weight loss. Bupropion is thought to stimulate the release of α -MSH from proopiomelanocortin (POMC) neurons in the arcuate nucleus in the hypothalamus, which leads to downstream effects on feeding behavior (i.e., decreased food consumption) and energy utilization. Whereas naltrexone is thought to block the inhibitory feedback loop mediated by β -endorphin at mu opioid receptors on POMC neurons to facilitate a more potent and longer-lasting activation of POMC neurons. Bupropion and naltrexone may also act synergistically via the ventral tegmental nucleus (VTA) in the mesolimbic system, which mediates many goal-directed behaviors. Dopamine and endogenous opioid peptides are key neurotransmitters influencing the activity of this pathway.

Orexigen Therapeutics Inc. did not conduct a nonclinical development/animal toxicology program. This 505(b)(2) application relies primarily on the Agency findings of the safety and efficacy as reflected in the approved product labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl). The right of reference for the nonclinical data in either NDA 18-932 for ReVia[®] (naltrexone HCl) or NDA 20-358 for Wellbutrin SR[®] (bupropion HCl) was not obtained. Extensive nonclinical studies have already been conducted to support the approval of naltrexone for the treatment of substance abuse and of bupropion for the treatment of major depressive disorder. Similar to obesity, the currently approved clinical indications for bupropion and naltrexone require chronic pharmacological treatment. Therefore, only an evaluation of naltrexone on electrical conductance at hERG channels was conducted in support of the application, as requested by the Agency. Relevant published literature findings on the pharmacology, pharmacokinetics, and toxicology of both drugs were also provided for review.

A bridge between the reference listed drugs (ReVia[®] [naltrexone HCl] and Wellbutrin SR[®] [bupropion HCl]) and the FDC drug product of naltrexone HCl and bupropion HCl was established through CMC data in lieu of conducting additional nonclinical studies. In concurrence with the CMC staff, the impurities and degradants present in the drug substances and drug product did not require qualification via bridging nonclinical toxicology studies based on ICH Q3A and Q3B guidances. Potentially genotoxic impurities were identified in naltrexone (b)(4) potential process impurity) and bupropion (b)(4) chemical intermediate) based on structural alerts. Although the proposed specifications for each potentially genotoxic metabolite will yield a total daily intake of (b)(4) μ g, which is (b)(4) the threshold of toxicological concern (TTC) for genotoxic impurities, it is reasonable to conclude that the impurities have been adequately qualified in the genotoxicity and carcinogenicity studies described in the labels of the reference listed drugs. Moreover, there are no novel excipients present in the drug product that would require qualification.

1.2 Brief Discussion of Nonclinical Findings

Nonclinical studies with the FDC drug product were not performed.

The nonclinical ADME properties and pharmacokinetics (PK) of naltrexone and bupropion were previously established individually. Studies conducted under the clinical program addressed the pharmacokinetics of the drug combination as well as possible drug-drug interactions between naltrexone and bupropion, naltrexone/bupropion tablets and other drugs, and naltrexone and other drugs.

The available nonclinical data in the published literature suggest that the clinical increases in heart rate and blood pressure caused by the FDC drug product are attributable to the sympathomimetic activity of bupropion. At clinically relevant doses in dogs, bupropion (3-10 mg/kg; 60-200 mg/m²; 0.5-1.5X MHRD of 360 mg bupropion; mg/m² basis) caused transient elevations in pulmonary vascular resistance index and mean pulmonary arterial pressure (Paganelli et al., 2006a; Paganelli et al., 2006b), possibly as a result of stimulation of alpha-adrenoceptors in the pulmonary circulation by dopamine (DA). Small changes in systemic vascular resistance index (SVRI), heart rate, and mean arterial pressure were also noted in dogs following a single dose of bupropion (60 mg/m²; 0.5X MHRD of 360 mg bupropion). Moreover, bupropion (1-30 μM; 0.3-8 μg/mL) exerted a dose-related positive inotropic response in human myocardium *in vitro* (Cremers et al., 2003) at concentrations approximately 2-50 times that of human mean peak plasma concentrations after repeat dosing (1-week; 32 mg naltrexone SR/360 mg bupropion SR; C_{max}=0.16 μg/mL). Naltrexone did not elicit similar cardiovascular/hemodynamic changes at clinically relevant doses. These studies with bupropion suggest that increases in pulmonary vascular resistance and pressure may be greater than the increases in mean pressure and pulse. The pressor effect of bupropion is well established from studies in animals and in humans. However, its contribution to cardiovascular risk may differ in the intended obese population that is already at an increased long-term risk of cardiovascular events, compared to the currently approved clinical indications for this drug.

The lack of inhibitory effects on hERG mediated I_{Kr} current with naltrexone and 6-β-naltrexol as established by the sponsor, and the lack of effect on G protein-activated inwardly rectifying K⁺ (GIRK) channels with bupropion *in vitro* as established by Kobayahsi et al. (2004) at concentrations exceeding human mean peak plasma concentrations (C_{max}) of both drugs suggests that the FDC drug product of naltrexone HCl and bupropion HCl will not cause QTc changes.

Based on the labeling of ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl) as well as the nonclinical published literature, there are no significant safety concerns regarding drug interactions between naltrexone and bupropion in terms of target organ toxicity.

Bupropion caused hepatotoxicity in both rats and dogs, as established in the Wellbutrin SR[®] label and published nonclinical studies (Tucker, 1983). In the 2-year rat study, bupropion caused an increase in hyperplastic nodules (non-neoplastic lesions), hepatocellular hypertrophy, focal hepatocellular hyperplasia, and liver weight at approximately 5X the MHRD of 360 mg bupropion (≥100 mg/kg; 600 mg/m²); a NOAEL was not established. In the 52-week dog study, there were reversible histological hepatic findings (centrilobular hepatocellular vacuolation, slight intrahepatic bile duct proliferation, slight centrilobular fibroplasia, and slight Kupffer cell proliferations) and clinical chemistry changes (↑ ALT, AST, and ALP) at ≥80 mg/kg (1600 mg/m²; ~12X MHRD of 360 mg bupropion). However, there is no *a priori* reason to suspect exacerbation of bupropion-related hepatocellular toxicity when co-administered with

naltrexone as there is no indication of nonclinical hepatocellular toxicity associated with naltrexone.

Studies in the published literature also established that bupropion elicits seizure activity/convulsions in mice (~3-4X MHRD 360 mg bupropion; mg/m² basis) and dogs (~2X MHRD of 360 mg bupropion; mg/m² basis) at doses near clinical exposure (Tutka et al., 2004; Tutka et al., 2005; van der Linde et al, 2010). The mechanism for this remains unresolved.

Information on the genotoxicity, carcinogenicity, and reproductive toxicity described in the reference listed drug labels for naltrexone and bupropion support the chronic administration of the FDC drug product of naltrexone HCl and bupropion HCl.

In the rat, naltrexone was associated with neoplastic findings (i.e., testicular mesotheliomas and tumors of vascular origin) for which a NOEL (30 mg/kg; 180 mg/m²; ~15X MHRD of 32 mg naltrexone) was established. At doses exceeding clinical exposure, bupropion caused no drug-related tumors in the 2-year rat and mouse studies.

Pregnancy Category 'C' is recommended for the FDC drug product given that both naltrexone and bupropion are labeled as Pregnancy Category 'C'. In rabbits, bupropion slightly increased the incidence of fetal malformations and skeletal variations in rabbits at all doses evaluated (≥ 25 mg/kg; 600 mg/m²; ~2X MHRD of 360 mg bupropion) and decreased fetal weights at 50 mg/kg and greater (600 mg/m²; ~5X MHRD of 360 mg bupropion). Naltrexone caused early fetal loss in rats at ≥ 30 mg/kg (180 mg/m²; ~15X MHRD of 32 mg naltrexone) and rabbits at ≥ 60 mg/kg (720 mg/m²/day; ~60X MHRD of 32 mg naltrexone). Only naltrexone was found to cause impairment of fertility. However, the clinical relevance of an increase in pseudopregnancy in the rat at approximately 50X the MHRD of 32 mg naltrexone (100 mg/kg; 600 mg/m²) is not known. The potential fertility and reproductive toxicity of 6- β -naltrexol was not established given that rats do not form appreciable quantities of the major human metabolite.

1.3 Recommendations

1.3.1 Approvability

AP (Approval)

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are required.

1.3.3 Labeling

For this 505(b)(2) application for which the sponsor did not conduct a nonclinical development/animal toxicology program, the language used in the label should be identical to the referenced drug labels of ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl). Safety margins in the proposed label were estimated using body surface area exposure (mg/m²) based on the body weight of $\frac{(b)}{(4)}$ kg. The safety margins have been corrected using a 100 kg body weight, which is appropriate for an obese population. Changes/additions to the proposed label are underlined.

5 WARNINGS AND PRECAUTIONS, 5.6 Hepatotoxicity

(b) (4)

In CONTRAVE clinical studies, (b) (4) there were no cases of elevated transaminases >3x ULN in conjunction with an increase in bilirubin >2x ULN.

8 USE IN SPECIFIC POPULATIONS, 8.1 Pregnancy

(b) (4)
Reproduction and developmental studies have not been conducted for (b) (4). Separate studies with bupropion and naltrexone have been conducted in pregnant rats and rabbits.

Naltrexone administered orally has been shown to increase the incidence of early fetal loss in rats administered ≥ 30 mg/kg/day (180 mg/m²/day) and rabbits administered ≥ 60 mg/kg/day (720 mg/m²/day), doses at least 15 and (b) (4) times, respectively, the maximum recommended human dose [MRHD] of the naltrexone component in CONTRAVE on a mg/m² basis. There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 200 mg/kg/day (approximately 100 and 200 times the recommended therapeutic dose, respectively, (b) (4)).

Bupropion was administered orally in studies conducted in rats and rabbits at doses up to 450 and 150 mg/kg/day, respectively (approximately 20 and (b) (4) times the MRHD, respectively, of the bupropion component in CONTRAVE on a mg/m² basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately 2 times the MRHD on a mg/m² basis) and greater. Decreased fetal weights were seen at 50 mg/kg and greater (approximately 5 times the MRHD on a mg/m² basis). When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately (b) (4) times the MRHD of the bupropion component in CONTRAVE on a mg/m² basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

13 NONCLINICAL TOXICOLOGY STUDIES, 13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility

In a two-year carcinogenicity study in rats with naltrexone, there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females. The incidence of mesothelioma in males given naltrexone at a dietary dose of 100 mg/kg/day (b) (4) times the recommended therapeutic dose on a mg/m² basis for the naltrexone maintenance dose for CONTRAVE) was 6%, compared with a maximum historical incidence of 4%. The incidence of vascular tumors in males and females given dietary doses of 100 mg/kg/day was 4%, but only the incidence in females was increased compared with a maximum historical control incidence of 2%. There was no evidence of carcinogenicity in a two-year dietary study with naltrexone in male and female mice.

Lifetime carcinogenicity studies of bupropion were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately (b) (4) and 3 times the maximum recommended human dose (MRHD) of the bupropion component in CONTRAVE, respectively, on a mg/m² basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 5 to (b) (4) times the MRHD of

the bupropion component in CONTRAVE on a mg/m² basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

There was limited evidence of a weak genotoxic effect of naltrexone in one gene mutation assay in a mammalian cell line, in the Drosophila recessive lethal assay, and in non-specific DNA repair tests with E. coli. However, no evidence of genotoxic potential was observed in a range of other in vitro tests, including assays for gene mutation in bacteria, yeast, or in a second mammalian cell line, a chromosomal aberration assay, and an assay for DNA damage in human cells. Naltrexone did not exhibit clastogenicity in an *in vivo* mouse micronucleus assay.

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1 of 3 *in vivo* rat bone marrow cytogenetic studies.

(b) (4) Naltrexone administered orally to rats caused a significant increase in pseudopregnancy and a decrease in pregnancy rates (b) (4) 100 mg/kg/day (approximately 50 times the MRHD of the naltrexone component in CONTRAVE on a mg/m² basis). There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.

A fertility study of bupropion in rats at doses up to 300 mg/kg/day (approximately (b) (4) times the MRHD of the bupropion component in CONTRAVE on a mg/m² basis) revealed no evidence of impaired fertility.

2 Drug Information

2.1 Drug

CAS Registry Number

Naltrexone HCl: 16676-29-2

Bupropion HCl: 31677-93-7

Code Name

Naltrexone HCl: (b) (4)

Bupropion HCl: (b) (4)

Chemical Name

Naltrexone HCl:

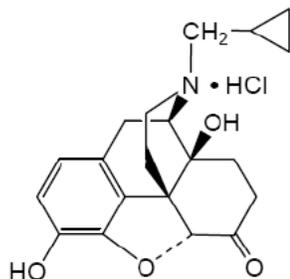
- Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy, hydrochloride, (5 α)- (USAN 1)
- 17-(Cyclopropylmethyl)-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one, hydrochloride (USAN 2, IUPAC)

Bupropion HCl:

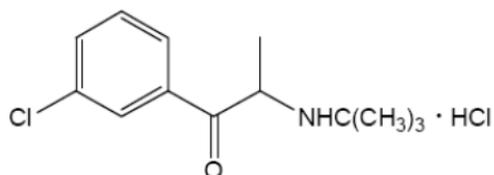
- 1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (1:1) (USAN 1)
- (2RS)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino] propan-1-one hydrochloride (USAN 2)
- (\pm)-2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one hydrochloride (IUPAC)
- (\pm)-2-(tert-butylamino)-3'-chloropropiophenone hydrochloride

Molecular Formula/Molecular WeightNaltrexone HCl: $C_{20}H_{23}NO_4 \cdot HCl$ ($C_{20}H_{24}ClNO_4$)/377.86Bupropion HCl: $C_{13}H_{18}ClNO \cdot HCl$ ($C_{13}H_{19}Cl_2NO$)/276.2**Structure or Biochemical Description**

Naltrexone HCl:



Bupropion HCl:

**Pharmacologic Class**Naltrexone is a μ (mu) opioid antagonist.

Bupropion is a biogenic amine reuptake inhibitor, mainly of dopamine (DA) and norepinephrine (NE).

2.2 Relevant NDAs and DMFsNDA 18-932 (ReVia[®], naltrexone HCl)NDA 20-358 (Wellbutrin SR[®]; bupropion HCl)

DMF (b) (4) Type II; (b) (4) naltrexone HCl)
 DMF (Type II; (b) (4) naltrexone HCl)
 DMF (Type II, (b) (4) bupropion HCl)
 DMF (Type II, (b) (4) bupropion HCl)

2.3 Drug Formulation

The FDC drug product (naltrexone HCl 4 or 8 mg and bupropion HCl 90 mg) is a combination drug product formulated as a film coated trilayer tablet for (b) (4) release oral delivery; bupropion HCl in one layer, an inert middle layer, and naltrexone HCl in the third layer. Both active pharmaceutical ingredients (bupropion HCl and naltrexone HCl) conform to the requirements of the respective current USP monographs. Two drug product strengths, which (b) (4)

Drug Product Unit Composition (8 mg/tablet Naltrexone HCl Presentation)

Ingredient	Amount			Function
	mg/ tablet	wt% of layer	wt% of tablet ¹	
(b) (4)				
Bupropion Hydrochloride USP	90.0		(b) (4)	Active ingredient
L-Cysteine Hydrochloride USP	(b) (4)			(b) (4)
Microcrystalline Cellulose (b) (4) NF				
Hydroxypropyl Cellulose (b) (4) NF				
Magnesium Stearate NF				
(b) (4)				
Microcrystalline Cellulose (b) (4) NF				(b) (4)
Lactose Anhydrous NF				
Crospovidone (b) (4) NF				
Magnesium Stearate NF				
FD&C Blue #2 Aluminum Lake				
(b) (4)				
Naltrexone Hydrochloride (b) (4) USP	8.0			Active ingredient
Microcrystalline Cellulose (b) (4) NF	(b) (4)			(b) (4)
Hypromellose USP (b) (4)				
Hydroxypropyl Cellulose (b) (4) NF				
Edetate Disodium USP				
Colloidal Silicon Dioxide NF				
Lactose Monohydrate (b) (4) NF				
Magnesium Stearate NF				
(b) (4)				
(b) (4)				(b) (4)
Opadry II Blue (b) (4)				
Overall total:	680		100	(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product. Each compendial excipient to be used in the proposed commercial drug product meets the requirements of the respective current USP or NF monograph.

2.5 Comments on Impurities/Degradants of Concern

Degradants

All known drug product degradants are characterized compounds, and are specified at or below the ICH Q3B(R2) qualification threshold and/or have been qualified at levels well above the specified limits from data in Wellbutrin SR[®] NDA 20-358 for which right of reference was obtained.

Impurities

Naltrexone

With the exception of (b) (4) a limit of NMT (b) (4) % has been established for individual specified impurities and NMT (b) (4) % for any unspecified impurity based on the maximum daily clinical dose of naltrexone (32 mg/day), which meets the ICH Q3A(R2) drug substance impurity qualification threshold. A limit of (b) (4) % (100 ppm) was proposed for the impurity (b) (4) (potential process impurity) that possesses the potentially genotoxic (b) (4)

Proposed Acceptance Criteria of Bupropion Impurities (Sponsor's Table)

Related Compounds:	(b) (4)	NMT (b) (4) %	USP monograph
		NMT %	
		NMT (b) (4) ppm	Type II DMF methods

2.6 Proposed Clinical Population and Dosing Regimen

The FDC drug product of naltrexone HCl and bupropion HCl is intended for the treatment of obesity and weight management for patients with an initial body mass index $\geq 30 \text{ kg/m}^2$ or $\geq 27 \text{ kg/m}^2$ with one or more risk factors (e.g., diabetes, dyslipidemia, or hypertension).

The recommended daily dose is two naltrexone HCl 8 mg/bupropion HCl 90 mg (8/90) sustained-release (SR) tablets twice daily for a total dose of 32 mg naltrexone and 360 mg bupropion. Dosing is escalated over a 3-week period until achieving the total daily maintenance dose. Treatment initiation and escalation with naltrexone HCl 4 mg/bupropion HCl 90 mg (4/90) SR tablets may be considered.

2.7 Regulatory Background

As an oral monotherapy, naltrexone HCl was approved in 1984 for the treatment of opioid addiction and for alcohol dependence in 1995. In 2006, an injectable, extended-release formulation of naltrexone was approved for alcohol dependence. Of the approved naltrexone drug products, ReVia[®] (50 mg naltrexone HCl tablet) was selected as the reference listed drug as it was determined to be the closest pharmaceutical equivalent to that in the FDC drug product of naltrexone HCl/bupropion HCl with respect to dosage strength and route of administration.

Bupropion HCl was first approved as an antidepressant in 1985 (Wellbutrin[®]). Sustained-release formulations were approved in 1996 (Wellbutrin SR[®]; twice daily dosing) and 2003 (Wellbutrin XL[®]; once daily dosing). In 1997, a controlled-release formulation of bupropion HCl was approved as an aid to smoking cessation (Zyban[®]). A hydrobromide salt of bupropion (Aplenzin[™]) was also approved for the treatment of depression. Wellbutrin SR[®] (bupropion HCl) was selected as the most appropriate reference listed drug for this application as it was determined to be the closest pharmaceutical equivalent with respect to dosage strength and route of administration. The usual adult target dose for Wellbutrin SR[®] is 300 mg/day, administered as 150 mg twice daily. An increase in dosage to the maximum of 400 mg/day, given as 200 mg twice daily, may be considered after several weeks of treatment at 300 mg/day.

3 Studies Submitted

3.1 Studies Reviewed

This is a 505(b)(2) submission. The sponsor is primarily referencing the Agency's previous findings of safety and efficacy for ReVia[®] (naltrexone HCl; NDA 18-932) and Wellbutrin SR[®] (bupropion HCl; NDA 20-358) to support the preclinical safety of the FDC drug product of naltrexone HCl and bupropion HCl. The sponsor also provided published literature to support the preclinical safety of the FDC drug product. Orexigen Therapeutics Inc. conducted one *in vitro* study to assess the effects of naltrexone and 6- β -naltrexol on the rapidly activating inward rectifying potassium current (I_{Kr}) conducted by hERG (human ether-a-go-go related gene) channels stably expressed in a HEK293 cell line, as agreed upon in the Type C Meeting (24 April 2006) as part of the evaluation of safety pharmacology..

1560-001	Evaluation of the Effects of Naltrexone and 6-Betanaltrexol on Cloned hERG Channels expressed in Human Embryonic Kidney Cells
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3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

In support of this 505(b)(2) new drug application, one safety pharmacology study was conducted to assess the effects of naltrexone and 6- β -naltrexol on the rapidly activating inward rectifying potassium current (I_{Kr}) conducted by hERG channels. No other nonclinical pharmacology studies were conducted for this 505(b)(2) submission. The review relied upon information from the approved labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl), as well as information from the published literature.

4.1 Primary Pharmacology

No new nonclinical primary pharmacology studies were conducted for this 505(b)(2) submission.

Mechanism of Action

Naltrexone

Naltrexone is a pure opioid antagonist. Naltrexone binds with very high affinity to the mu subtype (Gulya et al., 1986), but also has substantial affinity for kappa and delta receptors. The primary metabolite of naltrexone, 6- β -naltrexol, also acts as an opioid antagonist. Although 6- β -naltrexol is substantially less potent than naltrexone, it attains concentrations higher than those of naltrexone (~30X higher) and remains longer in the systemic circulation than naltrexone (4h versus 13h) (Meyers et al., 1984), which may contribute to the overall pharmacological activity of the drug.

The primary pharmacology of naltrexone is mediated by occupation and competitive blockade of opioid receptors (Pert et al., 1973), antagonizing the effects of both exogenous opioids and endogenous opioid neurotransmitters. According to the approved label for ReVia[®] (naltrexone HCl):

[Naltrexone] markedly attenuates or completely blocks, reversibly, the subjective effects of intravenously administered opioids. When co-administered with morphine, on a

chronic basis, ReVia blocks the physical dependence to morphine, heroin and other opioids.

In addition to its approved use for opioid dependence, naltrexone is also approved for the treatment of alcohol dependence. Naltrexone is thought to block the reinforcing effects of alcohol, as alcohol promotes the release of endogenous opioids in brain reward pathways.

Nonclinical studies have shown naltrexone decreases food and fluid intake in animals. Naltrexone reduces food and water intake in rats when administered acutely or chronically (Marks-Kaufman et al., 1984; Kirkham et al., 1987). Kirkham et al. (1987) demonstrated that naltrexone (SC) significantly reduced consumption of the saccharin-glucose solution (1-10 mg/kg; 6-60 mg/m²; ~0.5-5X MHRD of 32 mg naltrexone), and of sweet (10 mg/kg) and oily palatable mashes (1-10 mg/kg) in food deprived and non-deprived rats. Reduction in appetitive behaviors by mu opioid antagonists is thought to be mediated by antagonism of hypothalamic opioid autoreceptors involved in the regulation of homeostasis. Interactions with endogenous opioids involved in reward neurocircuitry may also mediate the effects of naltrexone on food intake. Stimulation of feeding behavior by direct injection of the selective mu agonist Tyr-D-Ala-Gly-(Me)Phe-Gly-ol (DAMGO) into the mesolimbic reward pathway, was reversed by naltrexone (MacDonald et al., 2003).

Bupropion

Bupropion is a moderately effective reuptake inhibitor of dopamine (DA) and norepinephrine (NE) through the blockade of the DA and NE reuptake transporters (Ferris et al., 1982; Ferris and Beaman, 1983; Ascher et al., 1995) with weak binding affinity and low potency at the serotonin (5-HT) reuptake transporter (Ferris et al., 1982; Richelson and Pfenning, 1984; Tatsumi et al., 1997). The two major metabolites of bupropion (hydroxybupropion [306U73] and threohydrobupropion [494U73]) also inhibit DA and NE reuptake suggesting that the metabolites may contribute meaningfully to the drug's therapeutic activity. Although hydroxybupropion [306U73] and threohydrobupropion [494U73] are approximately 7- to 20-fold weaker than bupropion as a DA reuptake inhibitor, concentrations of the bupropion metabolites were generally higher than those of bupropion following acute and repeat dosing in humans (Report AA88068; Study NB-236) and animals (Welch et al., 1987). As inhibitors of NE reuptake, bupropion and hydroxybupropion [306U73] have comparable potencies (IC₅₀=4-7 μM). Bupropion and its two major metabolites (hydroxybupropion and threohydrobupropion) have been reported to have weak or negligible binding affinity for an array of neuronal receptors, including dopaminergic D1 and D2, serotonergic 5-HT1A and 5-HT2A, adrenergic α1, α2 and β, and muscarinic cholinergic or histamine H1 receptors (Hall et al., 1984; Sanchez and Hyttel, 1999).

NE, 5-HT, and DA Reuptake Inhibition by Bupropion and Major Metabolites in Synaptosomal Preparations of Rat and Mouse Brain Areas

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Source: Ascher et al. (1995) ; Table 1

Bupropion is approved for the treatment of depression and is presumably efficacious via noradrenergic and/or dopaminergic mechanisms. Bupropion is also approved as an aid to smoking cessation. Bupropion interacts with the nicotinic cholinergic system as a functional antagonist at centrally expressed nicotinic receptor subtypes (i.e., $\alpha 3\beta 2$, $\alpha 4\beta 2$ and $\alpha 7$) and has been reported to attenuate the pharmacological and conditioned reinforcing properties of nicotine in animal models presumably by mediating changes in DA neurotransmission in brain reward pathways.

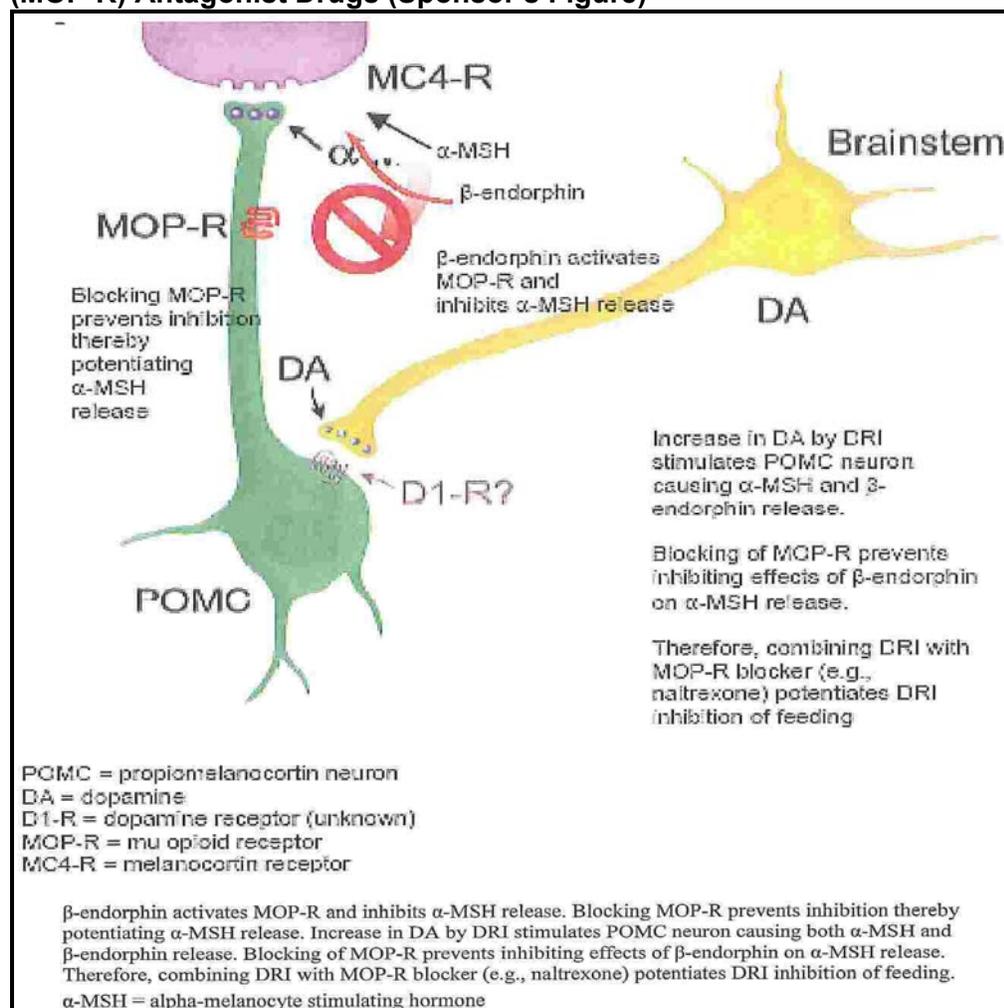
There is also data that indicate that bupropion affects energy balance. In rats, bupropion (IP; 25-75 mg/kg; 150-450 mg/m²; ~1-3X MHRD of 360 mg bupropion) caused a dose-dependent decrease in food consumption, while pretreatment with the DA receptor blocker pimozide reduced bupropion's anorectic response (Zarrindast and Hosseini-Nia, 1988). Billes and Cowley (2007) demonstrated that acute administration bupropion (IP; 40-80 mg/kg; 120-240 mg/m²; ~2-4X MHRD of 360 mg bupropion), the selective NE reuptake inhibitor nisoxetine, and the selective DA reuptake inhibitor GBR12783, individually, caused a transient (1-2 hr post dose) reduction food intake in both lean and obese mice. Additionally, the reduction in food intake following co-administration of nisoxetine and GBR12783 was additive suggesting that both DA and NE contribute to the anorectic effects of bupropion. Subchronic co-administration of nisoxetine and GBR12783 produced a transient, non-additive effect on food intake, and an additive reduction in body weight (8-10%). Nonclinical evidence also suggests that bupropion increases energy expenditure in rodents by increasing thermogenesis and locomotor activity (Liu et al., 2004; Billes and Cowley, 2008). Liu et al. (2004) demonstrated a potent acute thermogenic effect of bupropion (PO; 30 mg/kg; 180 mg/m²; ~1X MHRD of 360 mg bupropion) in rats, as evidenced by a rapid and sustained increase in oxygen consumption. D1/D2 receptor blockade significantly attenuated the bupropion-induced thermogenesis. Bupropion-induced thermogenesis was further demonstrated by increases in interscapular temperature induced by subchronic bupropion infusions (10 mg/kg/hr) over a 1-week period (Billes and Cowley, 2008).

Drug Activity Related to Proposed Indication

Although the exact neurochemical appetite suppression effects of the FDC drug product of naltrexone HCl and bupropion HCl have not fully been established, nonclinical studies suggest that the combination of naltrexone and bupropion has a synergistic action on two distinct sites of

the central nervous system that influence energy balance (food intake and energy expenditure): the hypothalamus and the mesolimbic dopamine circuit (reward system). The arcuate nucleus of the hypothalamus in the brain is an important site for regulating energy balance. Within the hypothalamus, DA appears to regulate the release and levels of neuropeptide Y (NPY), which plays a role in the stimulation of feeding. In rats, DA agonists (e.g., amphetamine) decreased feeding behavior through an antagonistic action on the hypothalamic NPY neurons (Gillard et al., 1993; Kuo, 2003). A second group of neurons in the arcuate nucleus, the pro-opiomelanocortin (POMC) neurons, secrete α -melanocyte-stimulating hormone (α -MSH), which decreases food intake and increases energy expenditure by acting on the melanocortin-4 receptors (MC4) (Cowley et al., 1999). The DA/NE reuptake inhibitory properties of bupropion are proposed to stimulate the release of α -MSH from POMC neurons in the arcuate nucleus, which leads to downstream effects on feeding behavior and energy utilization. The activity of POMC neurons is also subject to regulation by opioid autoreceptors. Beta-endorphins, which are simultaneously released with α -MSH, are an endogenous agonist of the mu opioid receptor on POMC neurons, which decrease the activity of POMC neurons and inhibit the release of α -MSH. Blocking this inhibitory feedback loop with naltrexone is proposed to facilitate a more potent and longer-lasting activation of POMC neurons, thereby amplifying the effects of bupropion on energy balance.

Potential of DA Reuptake Inhibitor (DRI) Feeding Inhibition by Mu-Opiate Receptor (MOP-R) Antagonist Drugs (Sponsor's Figure)



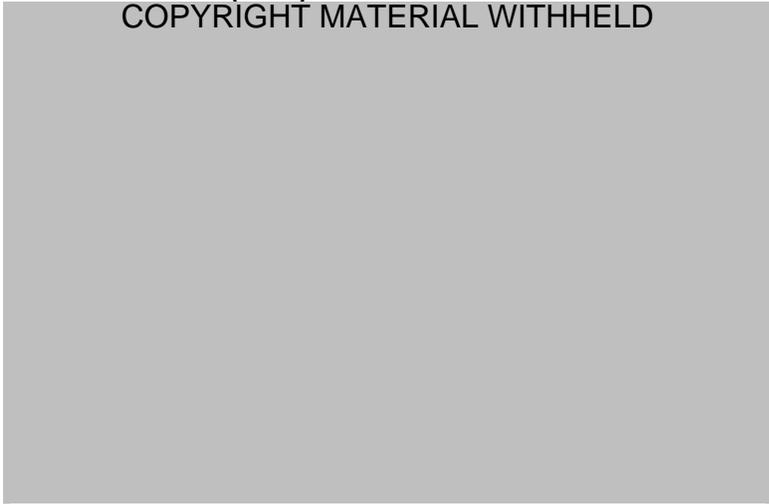
Independently and in combination, bupropion (10 $\mu\text{mol/L}$), likely through increases in brain levels of DA and NE, and naltrexone (1 $\mu\text{mol/L}$), likely through removal of tonic β -endorphin-mediated inhibition of POMC neurons, caused a transient increase in the frequency of action potentials in POMC neurons in hypothalamic slices from POMC-enhanced green fluorescent protein mice with the combination having a greater effect than either drug alone (Greenway et al., 2008). In lean mice on a normal diet, bupropion (IP; 1.5-90 mg/kg; ID_{50} of ~ 35 mg/kg) and naltrexone (IP; 1.5-30 mg/kg; ID_{50} of ~ 3.3 mg/kg) separately caused transient, dose-dependent decreased food intake peaking approximately 1 hour post injection. Co-administration of bupropion (IP; 20 mg/kg; 60 mg/m²; $\sim 0.5\text{X}$ MHRD of 360 mg bupropion) and naltrexone (IP; 1 mg/kg; 3 mg/m²; $\sim 0.3\text{X}$ MHRD of 32 mg naltrexone) in fasted lean and obese mice fed a high-fat diet produced a substantially greater decrease in food intake (~ 1 -4 hr postdose) than either compound administered alone, suggesting that the drugs act synergistically (Greenway et al. 2008).

The mesolimbic reward pathway, which mediates many goal-directed behaviors (Koob and Nestler, 1997; Nestler, 2005), represents a second mechanism through which bupropion and naltrexone may act synergistically on feeding behavior. The ventral tegmental nucleus (VTA) in the mesolimbic system contains DA cell bodies that project to the nucleus accumbens, a brain

area critically involved in mediating reward. Microinjection of bupropion (1 µg) and naltrexone (1 µg), alone and in combination, directly into the VTA in lean fasted mice (n=8) significantly decreased short-term food intake and the combination produced a statistically larger effect than either drug alone (Sinnayah et al., 2007).

Effects of Intra-VTA Injections of Bupropion (BUP) and Naltrexone (NAL) on Food Intake in Lean Mice

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Asterisks indicate a statistically significant ($p < 0.05$) decrease in food intake relative to saline condition. Source: Sinnayah et al. (2007)

4.2 Secondary Pharmacology

No new nonclinical secondary pharmacology studies were conducted for this 505(b)(2) submission.

Neuroendocrine/Hormonal Effects

Naltrexone and bupropion have modest indirect effects on neuroendocrine function in rats. Although the effects of co-administration of naltrexone and bupropion were not studied, studies in the published literature have shown that individually naltrexone and bupropion decreased prolactin, and that naltrexone increased luteinizing hormone (LH).

In rats administered naltrexone (1 mg/kg; 6 mg/m²; ~0.5X MHRD of 32 mg naltrexone) via an intracardiac catheter, there was a transient increase in LH (~1 hr postdose) and decrease in prolactin that was attributed to inhibition of endogenous opioid peptides, which control the secretion of prolactin and LH (Yogev et al., 1985). In male talapoin monkeys, a slightly lower dose of naltrexone (0.5 mg/kg; 4 mg/m²; ~0.3X MHRD of 32 mg naltrexone) administered by intra-muscular injection (2X daily for 2 weeks) was not associated with a decrease in prolactin levels, but did cause a reversible increase in LH, testosterone, and cortisol (Meller et al., 1980).

Bupropion (IP; 17 mg/kg; 102 mg/m²; ~0.8X MHRD of 360 mg bupropion) also significantly decreased prolactin concentrations in rats with a maximum effect (75% ↓) 100 minutes after injection with no significant effect on ACTH, corticosterone, or growth hormone (Piacentini et al., 2003). The decrease in prolactin was attributed to tonic inhibition by DA.

4.3 Safety Pharmacology

In support of this 505(b)(2) new drug application, one *in vitro* study was conducted to assess the effects of naltrexone and 6β-naltrexol on the rapidly activating inward rectifying potassium

current (I_{Kr}) conducted by hERG channels. Additional information pertaining to the cardiovascular and neurologic safety pharmacology of naltrexone and/or bupropion was obtained from the approved labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl), as well as the published literature.

Neurological Effects

Through an undetermined mechanism, bupropion use and overdose is associated with an increased risk of seizures. According to the approved label for Wellbutrin SR[®] (bupropion HCl):

Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in the selection of patients treated with Wellbutrin SR.

At doses of Wellbutrin SR up to a dose of 300 mg/day, the incidence of seizure is approximately 0.1% (1/1000) and increases to approximately 0.4% (4/1000) at the maximum recommended dose of 400 mg/day.

Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.

[Other] circumstances associated with an increased seizure risk include, among others, excessive use of alcohol; abrupt withdrawal from alcohol or other sedatives; addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.

Recommendations for Reducing the Risk of Seizure: Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if

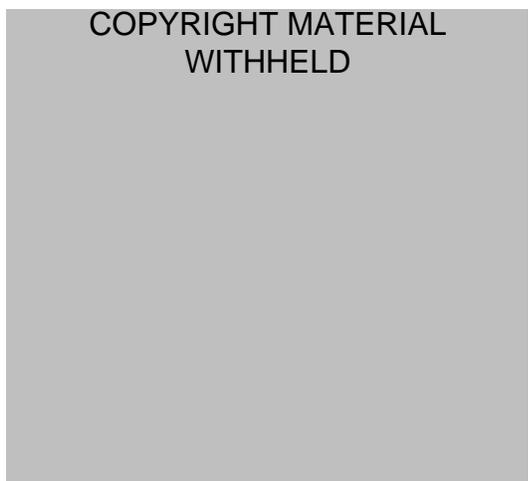
- the total daily dose of Wellbutrin SR Tablets does *not* exceed 400 mg,
- the daily dose is administered twice daily, and
- the rate of incrementation of dose is gradual.
- no single dose should exceed 200 mg to avoid high peak concentrations of bupropion and/or its metabolites

A published study by Tutka et al. (2004) further investigated the convulsant effects of bupropion in male Swiss mice (n=8 per dose group). Bupropion (IP; 100-160 mg/kg) dose-dependently produced clonic convulsions with the convulsive dose₅₀ (CD₅₀) being 119.7 mg/kg (359 mg/m²; ~3X MHRD of 360 mg bupropion) and the CD₉₇ being 156.7 mg/kg (470 mg/m²; ~4X MHRD of 360 mg bupropion). Convulsions were preceded by hyperactivity, chewing, head movements, and balance impairment. Tonic convulsions were occasionally observed in animals (1/8 mice) dosed at 140 mg/kg or 160 mg/kg (420-480 mg/m²; ~3-4X MHRD 360 mg bupropion). A subsequent study in male Swiss mice demonstrated that the anti-epileptic drugs clonazepam [ED₅₀=0.06 mg/kg] and gabapentin [ED₅₀=34.5 mg/kg] produced a dose-dependent protective effect against clonic convulsions induced by bupropion (IP) at the CD₉₇ dose of 139.5 mg/kg (419 mg/m²; ~3X MHRD of 360 mg bupropion) without producing significant motor impairment (Tutka et al., 2005).

Moreover, in fentanyl/etomidate-anaesthetised dogs (n=6), an infusion of bupropion (0.5 mg/kg/min) for a maximum of 40 minutes induced EEG spiking in four of six dogs (van der Linde et al, 2010). In two dogs, seizures were observed at 10 mg/kg and 16 mg/kg with

durations of 58 seconds and 55 seconds, respectively. The established seizure threshold was determined to be 13 mg/kg (260 mg/m²; ~2X MHRD of 360 mg bupropion).

EEG Spiking after Bupropion Treatment in FEAB Dogs



Source: van der Linde et al. (2010)

Cardiovascular Effects

The labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl) do not discuss any nonclinical cardiovascular effects associated with either naltrexone or bupropion. However, the labels do mention several clinical cardiovascular effects associated with naltrexone (increased blood pressure, non-specific ECG changes, palpitations, tachycardia) and bupropion (hypertension [in some cases severe], palpitations, postural hypotension, stroke, tachycardia, vasodilation, complete atrioventricular block, extrasystoles, myocardial infarction, phlebitis, and pulmonary embolism).

A search of the published literature identified several nonclinical studies establishing the *in vitro* and *in vivo* responses relevant to the cardiovascular safety of naltrexone and bupropion. Additionally, the sponsor conducted one safety pharmacology study (*in vitro* naltrexone hERG evaluation) to support the development of the FDC drug product of naltrexone HCl and bupropion HCl (End-of-Phase-2 meeting; 1 October 2007).

Naltrexone

In support of the development of Contrave, Orexigen Therapeutics Inc. conducted an *in vitro* study to assess the effects of naltrexone and 6- β -naltrexol on the rapidly activating inward rectifying potassium current (I_{Kr}) conducted by hERG (human ether-a-go-go related gene) channels stably expressed in a HEK293 cell line.

EVALUATION OF THE EFFECTS OF NALTREXONE AND 6-BETA NALTREXOL ON CLONED HERG CHANNELS EXPRESSED IN HUMAN EMBRYONIC KIDNEY (HEK293) CELLS (1560-001) - GLP

Study No.: 1560-001
 Study Report Location: EDR
 Conducting Laboratory and Location: (b) (4)
 Date of Study Initiation: 14 March 2008
 GLP Compliance: Yes
 QA Statement: Yes
 Drug, Lot #, and % Purity: Naltrexone Hydrochloride Dihydrate, lot# 1351727, ≥99%
 6-Beta Naltrexol Hydrate, 016K4613, ≥96%

Key Study Findings

- Naltrexone (0.02-0.3 μM; 0.008-0.1 μg/mL) and 6-β-naltrexol (0.3-3 μM; 0.1-1 μg/mL) produced no appreciable inhibition of hERG mediated potassium currents.
- The highest concentrations of naltrexone (3 μM; 1 μg/mL) and 6-β-naltrexol (10 μM; 3 μg/mL) produced only slight inhibition of hERG mediated potassium currents (~6%); calculation of IC₅₀ values for hERG inhibition were not possible.

Reviewer's Notes

Given that the human mean peak plasma concentrations (C_{max}) of naltrexone and 6-β-naltrexol are 0.003 μg/mL and 0.052 μg/mL, repetitively, following repeat dosing (1-week) with Contrave tablets (32 mg naltrexone SR/360 mg bupropion SR), the predicted margins of safety are ~330X for naltrexone and ~60X for 6-β-naltrexol providing a more than adequate margin of safety with respect to inhibition of the hERG current.

Methods

HEK293 cells cotransfected with the hERG potassium channel cDNA and G418-resistant gene incorporated into a modified pCDNA3 plasmid were obtained from (b) (4) January at the (b) (4). The stable transfectants were held at a potential of -80 mV and hERG-mediated currents were evoked by application of a depolarizing voltage command step to +40 mV for 2 seconds followed by a repolarizing command step to -50 mV for 1.5 seconds; this was repeated once every 10 seconds. Peak tail currents from the last 30 seconds of the baseline period were averaged and compared to 30 seconds of data recorded in the presence of the test solutions. Current inhibition is reported in percent according to Inhibition (%) = 100*(1-(I_{test}/I_{baseline})) where I_{test} was the peak tail current measured in the presence of the test solution, and I_{baseline} was the peak tail current measured prior to exposure to the test solution; each cell served as its own control. The concentration levels for the treated groups were 0.02, 0.1, 0.3, and 3 μM naltrexone, and 0.3, 1, 3, and 10 μM 6-β-naltrexol. PSS containing 0.1% DMSO and cisapride (0.1 μM) were used as the vehicle control and positive control, respectively. Three to four replicates were tested at each concentration.

Results

Perfusion of naltrexone at 0.02-0.3 μM and 6- β -naltrexol at 0.3-3 μM produced no appreciable inhibition of hERG mediated potassium currents. Perfusion of naltrexone at a concentration of 3 μM or 6- β -naltrexol at 10 μM produced only slight inhibition of hERG mediated potassium currents (~6%). IC_{50} values for hERG inhibition were not possible to calculate. The concentrations of naltrexone and 6- β -naltrexol potentially required to evoke a 50% inhibition of the hERG current would exceed the therapeutic peak plasma concentrations. Therefore, neither naltrexone nor 6- β -naltrexol is considered to be potent hERG channel blockers.

The negative and positive controls used in this study clearly demonstrated the ability of the *in vitro* test system to detect an effect on the hERG channel mediated potassium current. Perfusion of PSS containing 0.1% DMSO (negative control vehicle) produced no appreciable inhibition of hERG mediated potassium currents. Whereas, perfusion of 0.1 μM cisapride (positive control article) produced approximately 78% inhibition of hERG channel mediated potassium currents.

Evaluation of the Effects of Naltrexone and 6 β -Naltrexol on Cloned hERG Channels Expressed in HEK293 Cells (Sponsor's Table)

Test Article Concentration	hERG Current Inhibition, % (mean)	SEM	N
0 μM (PSS with 0.1% DMSO)	0.51	0.273	3
0.02 μM Naltrexone ¹	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 β -Naltrexol ²	0.20	0.704	3
1 μM 6 β -Naltrexol	-0.31	0.109	3
3 μM 6 β -Naltrexol	0.06	0.185	3
10 μM 6 β -Naltrexol	5.78	1.054	4
0.1 μM Cisapride	77.95	1.537	3

¹Naltrexone hydrochloride dihydrate obtained from (b) (4) Lot number 1351727
²6 β -Naltrexol hydrate obtained from (b) (4) Lot number 016K4613
PSS = Physiological Salt Solution
DMSO = Dimethyl sulfoxide
SEM = Standard Error
Source: (b) (4) Study Report

In addition to the lack of significant inhibition of I_{Kr} in the *in vitro* hERG evaluation, naltrexone (0.001-10 $\mu\text{g}/\text{mL}$) was without significant effect on the cardiac action potentials of isolated sheep Purkinje fibers at concentrations exceeding the human mean peak plasma concentrations after repeat dosing (1-week; 32 mg naltrexone SR/360 mg bupropion SR; 0.003 $\mu\text{g}/\text{mL}$) (McIntosh et al., 1992).

In rats, naltrexone (SC; 20 mg/kg; 120 mg/m²; ~10X MHRD of 32 mg naltrexone) administered for 4 weeks had no effect on heart rate or arterial blood pressure (Tavakoli et al., 2007). In rabbits, naltrexone (IV; 3 mg/kg; 36 mg/m²; ~3X MHRD of 32 mg naltrexone) only decreased in heart rate in hypovolemic animals (experimental hypotension), but had no effect on pulse pressure, mean arterial pressure, or heart rate under baseline conditions (Schadt and York, 1982). Early evaluations tested the effects of 0.9 mg/kg of naltrexone (IV; 18 mg/m²; ~2X MHRD of 32 mg naltrexone) in the dog, and found it to be without effect on blood pressure, heart rate, respiration or body temperature (Blumberg and Dayton, 1973). A later study by Freye et al. (1983) found cumulative doses in dogs (IV; 0.001-0.08 mg/kg; 15 min intervals) induced modest dose-related bradycardia at 0.005-0.08 mg/kg (0.1-1.6 mg/m²; ~0.01-0.14X MHRD of 32 mg naltrexone) but did not affect on blood pressure, respiratory rate, arterial blood

gases, and EEG. Byrd (1983) demonstrated that acute dosing (IV; 0.3-10 mg/kg) in resting squirrel monkeys (n=6) produced a modest, transient increase in blood pressure (~5 mm Hg) at 10 mg/kg (70 mg/m²; ~6X MHRD of 32 mg naltrexone) lasting 5 minutes, but did not significantly affect heart rate (Byrd, 1983).

Effect of Naltrexone on Mean Arterial Blood Pressure and Heart Rate in Dogs

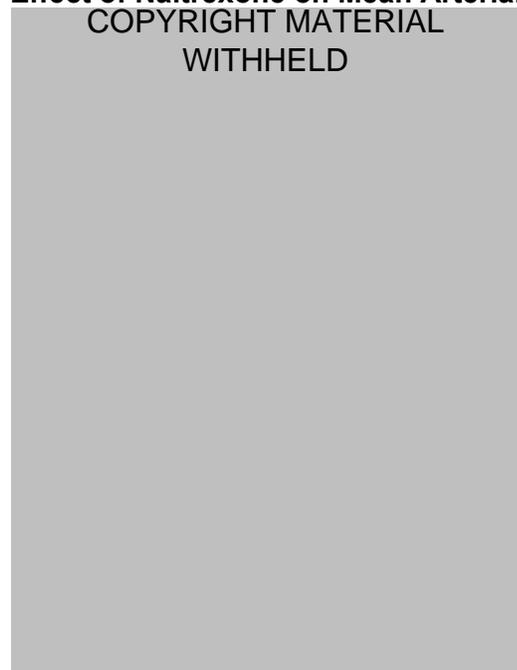
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Source: Freye et al. (1983); Figure 2

Effect of Naltrexone on Mean Arterial Blood Pressure and Heart Rate in Squirrel Monkeys

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Source: Byrd (1983); Figure 1

Overall, the available nonclinical data do not suggest that a 32 mg dose of naltrexone will cause any significant, clinically relevant cardiovascular effects. In squirrel monkeys, naltrexone caused a modest, transient increase in blood pressure in squirrel monkeys only at a dose (10 mg/kg) approximately 6 times the maximum recommended therapeutic maintenance dose (mg/m² basis) of naltrexone (32 mg), but not at lower doses (0.3-3 mg/kg; ~0.2-2X MHRD of 32 mg naltrexone). In rats and rabbits, at doses approximately 10 times and 3 times the maximum recommended therapeutic maintenance dose of 32 mg naltrexone (mg/m² basis), respectively, naltrexone did not elicit changes in heart rate or blood pressure. In dogs, naltrexone caused dose-related bradycardia (0.005-0.08 mg/kg; ~0.01-0.14X MHRD of 32 mg naltrexone), but did not affect blood pressure. Naltrexone was also without significant effect on cardiac action potentials in isolated Purkinje fibers (0.001-10 µg/mL) at concentrations

exceeding the human mean peak plasma concentrations after repeat dosing (1-week; 32 mg naltrexone SR/360 mg bupropion SR; 0.003 µg/mL). Moreover, the predicted margins of safety for naltrexone (up to ~330X at 3 µM [1 µg/mL]) and 6-β-naltrexol (up to ~60X at 10 µM [3 µg/mL]) were considered to be more than adequate with respect to inhibition of the hERG current at human mean peak plasma concentrations (C_{max}) of naltrexone (0.003 µg/mL) and 6-β-naltrexol (0.05 µg/mL) following repeat dosing.

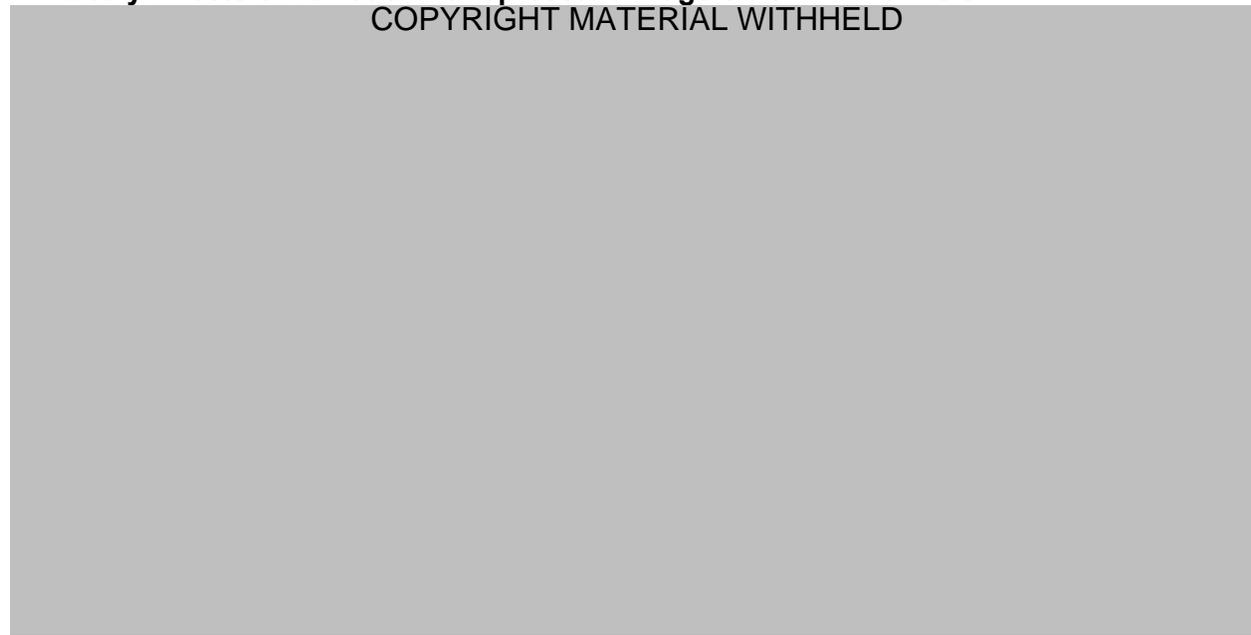
Bupropion

The Division concurred that there were adequate data characterizing the effects of bupropion on cardiac toxicity, and that additional testing of bupropion in a hERG channel assay was necessary in support of the development of Contrave (End-of-Phase-2 meeting; 1 October 2007). Several relevant published nonclinical studies documenting *in vitro* and *in vivo* responses relevant to the cardiovascular safety of bupropion were identified.

While there is no published data on the effects of bupropion on the hERG channel assay, Kobayahsi et al. (2004) conducted an *in vitro* study to determine the effects of bupropion on G-protein-activated inwardly rectifying K⁺ channels (GIRKs), including the cardiac-type GIRK1/4 channels, using a *Xenopus* oocyte expression assay; GIRK channels and the hERG channel have been shown to share the property of dose-dependent inhibition by tricyclic antidepressants and the atypical antidepressant maprotiline (Kobayahsi et al., 2004; Jo et al., 2000; Teschemacher et al., 1999; Jo et al., 2007). Bupropion (up to 100 µM; 28 µg/mL) had minimal effect on basal GIRK1/4 currents (4% inhibition of the 3 mM Ba²⁺-sensitive current component; n=8). Calculations of EC₅₀, IC₂₅, and IC₅₀ were not possible due to the lack of any significant inhibitory effect on the atrial GIRK channels. Given that human mean peak plasma concentrations (C_{max}) of bupropion are 0.16 µg/mL after repeat dosing (1 week) with Contrave (32 mg naltrexone/360 mg bupropion), the results of the study indicate that bupropion at the recommended maintenance dose (360 mg) is not expected to affect G protein-activated inwardly rectifying K⁺ channels.

Inhibitory Effects of Various Antidepressant Drugs on GIRK Channels

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Source: Kobayahsi et al. (2004); Table 1

Wang et al. (1981) conducted an *in vitro* assessment of the effects of bupropion in isolated tissues including (1) intracellular potentials of spontaneously beating isolated male Sprague-Dawley rat atria, (2) evoked action potentials from endocardial cells in isolated guinea pig atria, and (3) action potentials in isolated Purkinje fibers of adult male dog hearts. The effects of bupropion were compared to those of the tricyclic antidepressants amitriptyline and imipramine with known cardiac toxicity. In isolated rat atria (n=5-7), sinus rate decreased by 20% at 10 μ M bupropion (3 μ g/mL) and by 30% at 100 μ M bupropion (28 μ g/mL). In guinea pig atria (n=5-6), bupropion (10 μ M; 3 μ g/mL) reduced sinus rate and the amplitude of the action potentials while prolonging effective refractory period (ERP) and action potential duration at 100% repolarization (APD₁₀₀); amitriptyline and imipramine produced similar effects. In canine Purkinje fibers, bupropion caused a shortening of APD₅₀ (50% repolarization), but not APD₁₀₀; there was no effect on either action potential amplitude or *dv/dt* at doses at or below 10 μ M. Bupropion (100-300 μ M; 28-83 μ g/mL) also caused a slight reduction in resting potential, action potential amplitude, and *dv/dt* with little change in action potential duration in canine papillary muscle.

Another *in vitro* study using human right atrial muscle preparations demonstrated that bupropion (1-30 μ M; 0.3-8 μ g/mL) exerted a dose-related positive inotropic response (45% above basal levels at 30 μ M) (Cremers et al., 2003). The authors propose that this is possibly mediated by catecholamine release due to the indirect sympathomimetic properties of bupropion.

The hemodynamic effects of bupropion were studied in dogs (Cicardo et al., 1986; Paganelli et al., 2006a, 2006b). In anesthetized dogs (n=9), Cicardo et al. (1986) found bupropion (IV; 3-5 mg/kg; 60-100 mg/m²; ~0.5-0.8X MHRD of 360 mg bupropion) to have no effect on blood pressure or heart rate, and no effect on pressor responses elicited by IV injections of DA (30 μ g/kg), NE (1-2 μ g/kg), and serotonin (15 μ g/kg). In a more recent study, single bolus doses of bupropion (IV; 3 and 6 mg/kg; 60-120 mg/m²; ~0.5-0.9X MHRD of 360 mg bupropion) in dogs caused a significant transient increase in pulmonary vascular resistance index and mean pulmonary arterial pressure (1 min postdose), which returned to baseline within 10 minutes (Paganelli et al., 2006a). Cumulative doses of bupropion (IV; 0.01, 0.1, 1, 3, and 10 mg/kg) also caused an increase in mean pulmonary arterial pressure and pulmonary vascular resistance index following doses of 3 and 10 mg/kg (60-200 mg/m²; ~0.5-1.5X MHRD of 360 mg bupropion). However, bupropion (single and cumulative doses) had no significant effect on heart rate, mean arterial pressure, index cardiac, central venous pressure, and pulmonary capillary wedge pressure. In a follow-up study designed to evaluate combinations of bupropion and nicotine, Paganelli et al. (2006b) replicated the transient increase in pulmonary vascular resistance index and mean pulmonary arterial pressure following a single 3 mg/kg dose (IV; 60 mg/m²; ~0.5X MHRD of 360 mg bupropion) in dogs. There was also a transient, treatment-related increase in system vascular resistance index (SVRI), heart rate, and mean arterial pressure although the changes were not statistically significant.

Hemodynamic Effects of a Single Dose of Bupropion

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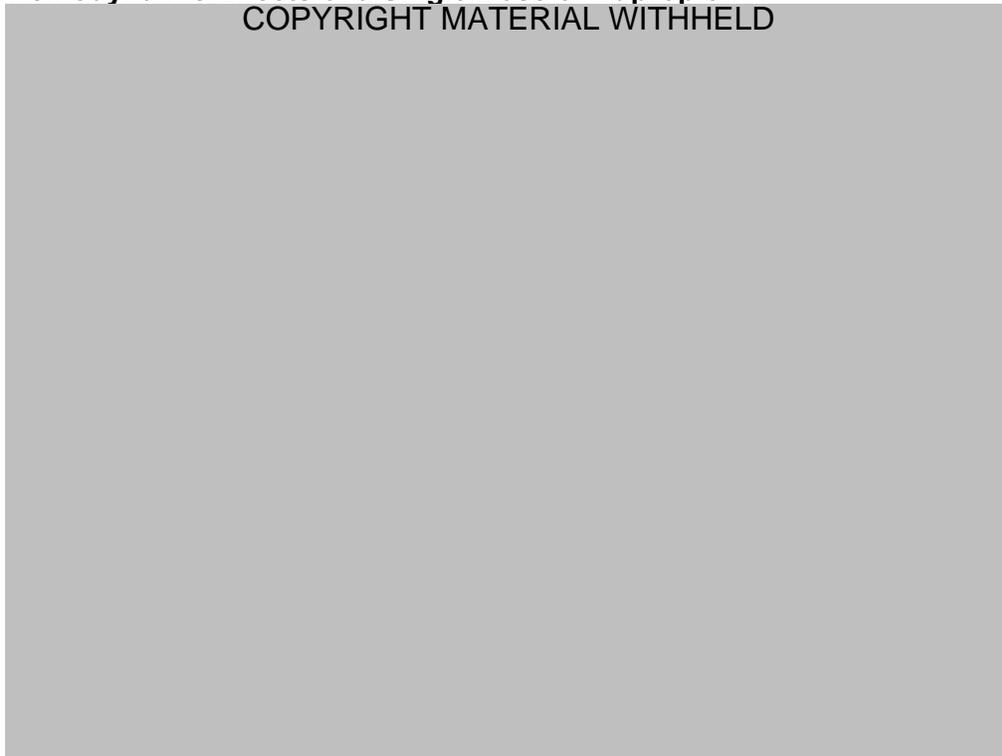


Figure 1. Heart rate (HR), cardiac index (CI), mean arterial pressure (MAP), and mean pulmonary arterial pressure (MPAP) at baseline (BL), and then 1, 10, and 20 min after the administration of 75 µg of nicotine/kg or an equal volume (10 mL) of saline, and 1, 10, and 20 min after the administration of 3 mg of bupropion/kg or an equal volume (10 mL) of saline in the saline/bupropion (open square), saline/nicotine (filled circle), nicotine/bupropion (filled square), and saline/saline (open circle) groups. The points are the mean ± SEM. * $p < 0.05$ vs BL. # $p < 0.05$ for saline/nicotine, nicotine/bupropion, and saline/bupropion vs. saline/saline group. Source: Paganelli et al. (2006b)

Overall, the nonclinical cardiovascular/hemodynamic changes associated with bupropion in published literature may be clinically relevant. *In vitro*, bupropion decreased sinus rate and had variable effects on action potential duration in isolated tissues at doses approximately 20-500 times human mean peak plasma concentrations after repeat dosing (1-week; 32 mg naltrexone SR/360 mg bupropion SR; C_{max} =0.16 µg/mL). Another *in vitro* study using human right atrial muscle preparations demonstrated that bupropion (1-30 µM; 0.3-8 µg/mL; ~2-50X of C_{max}) exerted a dose-related positive inotropic response (45% above basal levels at 30 µM) that the authors attributed the positive inotropic response to increased catecholamine release. Bupropion (single and cumulative dosing) also affected the hemodynamic parameters of the pulmonary system in dogs by transiently elevating the pulmonary pressure at clinically relevant doses (~0.5-1.5X MHRD of 360 mg bupropion; m^2/mg basis). Additionally, bupropion also caused a transient, treatment-related increase in system vascular resistance index (SVRI), heart rate, and mean arterial pressure in dogs following a single intravenous dose of 3 mg/kg dose (~0.5X MHRD of 360 mg bupropion; mg/m^2 basis), although the changes were not statistically significant.

Abuse Potential

The abuse and dependence potential of naltrexone and bupropion has been assessed by means of a critical evaluation of their chemical properties, dosage forms, biochemical activities, animal behavioral effects, pharmacokinetic, clinical pharmacology, adverse event profile, effects in psychometric tests reflective of abuse potential in healthy volunteers and drug abusers, and

other sources of information from marketed history of over 20 years for both products. The abuse potential assessment, submitted as a section of the NDA, is under review by the Controlled Substance Staff (CSS).

In brief, naltrexone is a pure opioid antagonist that produces aversive effects (opioid withdrawal symptoms) in opioid-dependent animals. Naltrexone has no intrinsic agonism at opioid receptors. Naltrexone does not lead to physical or psychological dependence, and tolerance to the opioid antagonist effect is not known to occur.

Bupropion is not a controlled substance. However, both clinical and nonclinical studies were conducted to assess the abuse and dependence potential of bupropion. The approved label for Wellbutrin SR[®] (bupropion HCl) contains the following information relating to the nonclinical abuse potential of bupropion:

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

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No new nonclinical pharmacokinetic/ADME/toxicokinetic studies were conducted for this 505(b)(2) submission. The nonclinical ADME properties and pharmacokinetics (PK) of naltrexone and bupropion, individually, were previously established. The ADME properties of naltrexone and bupropion are provided in the labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl), as well as in the published literature.

In lieu of nonclinical PK studies, clinical studies in the Phase 1 clinical program established the single-dose (two 8 mg naltrexone HCl/90 mg bupropion HCl tablets) and multiple-dose (two 8 mg naltrexone HCl/90 mg bupropion HCl tablets; twice daily for 1 week) PK profiles of naltrexone/bupropion tablets. These studies also collected ADME data on the main metabolites of naltrexone (6 β -naltrexol) and bupropion (hydroxybupropion, erythrohydrobupropion, and threo hydrobupropion).

In brief, naltrexone and bupropion are well absorbed, widely distributed (including the brain), and extensively metabolized by animals and humans. Following single oral administration of naltrexone/bupropion tablets to healthy subjects, peak concentrations of naltrexone and bupropion (T_{max}) occurred approximately 2 and 3 hours postdose. Both are subject to a large first-pass effect, leading to low absolute oral bioavailability (~4%). Bupropion and naltrexone are moderately bound to plasma proteins (naltrexone, 21%; bupropion; 84%). Naltrexone is metabolized primarily to the pharmacologically active 6 β -naltrexol by dihydrodiol dehydrogenases (DD1, DD2, and DD4) (Ohara et al., 1995; Porter et al., 2000). Two minor metabolites 2-hydroxy-3-O-methyl-6 β -naltrexol and 3-O-methyl-6 β -naltrexol also are detected in human plasma and urine (Wall et al. 1981). Naltrexone and 6 β -naltrexol are not thought to be subject to oxidative metabolism by CYP isoenzymes, but are subject to conjugation prior to excretion. Bupropion undergoes extensive hepatic metabolism and is biotransformed by

reductive metabolism in the liver to the pharmacologically active basic metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Bupropion is also transformed by side chain oxidative cleavage to the acidic metabolites *m*-chlorohippuric acid and *m*-chlorobenzoic acid, which are not considered to be pharmacologically active. CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while the CYP enzyme(s) responsible for the formation of threohydrobupropion and erythrohydrobupropion have not been elucidated. Naltrexone and bupropion, as well as their metabolites, are primarily excreted in urine with a lesser portion in feces. Naltrexone conjugates have also been found in bile, suggesting enterohepatic recycling (Garrett and El-Koussi, 1985; Reuning et al., 1989).

5.2 Drug-Drug Interactions

Several PK drug-drug interaction (DDI) findings are described in the Wellbutrin SR[®] label. Bupropion and its metabolites are inhibitors of CYP2D6 (Hesse et al., 2000; Reese et al., 2008), which may lead to clinically significant increases in exposure to drugs metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, venlafaxine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol) and Type 1C antiarrhythmics (e.g., propafenone, flecainide). There is also the potential for a drug interaction between bupropion and drugs that affect the CYP2B6 isoenzyme (e.g., orphenadrine, cyclophosphamide) given that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Additionally, co-administration of certain drugs that may induce the metabolism of bupropion (e.g., carbamazepine, efavirenz, lopinavir, rifampin) may decrease exposure to bupropion.

In support of this 505(b)(2) new drug application, the potential for DDIs between naltrexone and bupropion, between naltrexone/bupropion tablets and other drugs, and between naltrexone and other drugs were investigated using both *in vitro* and *in vivo* testing, as part of the clinical program.

To evaluate the potential for PK interactions between naltrexone and bupropion, a single-dose clinical study compared the relative bioavailability of naltrexone/bupropion tablets (two 8 mg naltrexone SR/90 mg bupropion SR tablets) to commercially available tablet formulations of naltrexone IR (50 mg) and bupropion SR (150 mg) in healthy adult subjects (Study NB-230). The single-dose PK profile of naltrexone/bupropion tablets was highly consistent with that of the approved individual components on a dose-adjusted basis indicating that the PK profile of the drug products are unaltered when administered in combination.

Three clinical drug-drug interactions studies were conducted to ascertain interactions between naltrexone/bupropion tablets (two 8 mg naltrexone SR/90 mg bupropion SR tablets administered once [single dose study] or BID [multiple dose study]) and antihypertensive agents (lisinopril [40 mg], nifedipine [90 mg], metoprolol [50 mg]), anti-diabetic agents (glyburide [6 mg]), and lipid-lowering agents (valsartan [320 mg] and atorvastatin [80 mg]). There were no PK interactions with valsartan and atorvastatin, or the antihypertensive lisinopril. Co-administration of naltrexone/bupropion tablets with the anti-hypertensive nifedipine resulted in increased exposure to naltrexone (24% ↑ in AUC and 58% ↑ in C_{max}) and bupropion (22% ↑ in C_{max}) that was just outside bioequivalence limits and therefore not considered to be clinically significant. Co-administration of naltrexone/bupropion with glyburide resulted in no change in glyburide PK parameters, but increased exposure to naltrexone (~2-fold ↑ in AUC and C_{max}) and bupropion (18% ↑ in AUC and 36% ↑ in C_{max}). However, because the glyburide was administered with a glucose solution to prevent hypoglycemia, the increased exposure is thought to be related to the administration of the glucose solution as opposed to a true DDI.

Steady-state dosing of naltrexone/bupropion resulted in a significant increase in metoprolol exposure (421% ↑ in AUC and 206% ↑ in C_{max}) relative to metoprolol alone, which was attributed to CYP2D6 inhibition by bupropion and its metabolites; metoprolol is a CYP2D6 substrate. Co-administration of metoprolol with naltrexone/bupropion tablets also slightly reduced naltrexone exposure (25% ↓ in AUC and 29% ↓ in C_{max}).

Using human liver microsomes, naltrexone caused no direct or time-dependent inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2E1, and CYP3A4, and modest direct or time-dependent inhibition of CYP2C9, CYP2C19, and CYP2D6 at high concentrations that are not clinically relevant. The metabolite 6β-naltrexol caused only modest time-dependent inhibition on CYP2C19 that is not considered to be clinically relevant. *In vitro* studies also demonstrated that naltrexone and 6β-naltrexol have little potential to induce the enzymatic activities of CYP1A2, CYP2B6, and CYP3A4 (isoforms chosen because of their potential to alter the exposure to bupropion). No *in vivo* studies were conducted given the lack of clinically relevant inhibition or induction of CYP P450 enzymes.

5.3 Other Pharmacokinetic Studies

Increases in mean serum creatinine with naltrexone HCl/bupropion HCl treatment compared to placebo in the Phase 3 studies. Two *in vitro* interaction studies were conducted to assess the potential for interaction of naltrexone and bupropion, as well as their major metabolites, with a kidney uptake transporter (renal organic cation transporter 2 [rOCT2]) that has been implicated in the secretion of creatinine. This transporter is found in the basolateral membrane of the renal tubule and promotes creatinine secretion. The potential of the test article to modify the uptake of metformin into the CHO cells expressing human rOCT2 was measured and compared to the accumulation in non-overexpressing cells (which allow for subtraction of nonspecific transport or diffusion) as well as comparing to the effects of vehicle and a positive control. Naltrexone (up to 2.2 μM; ~300X greater than clinical C_{max} [0.008 μM]) did not inhibit the human rOCT2-mediated metformin uptake, and 6β-naltrexol showed only modest dose-dependent inhibitory effect (~48% inhibition) at the highest concentration. (60 μM; ~300X greater than clinical C_{max} [0.15 μM]). Therefore, naltrexone and its metabolite are not thought to cause a clinically relevant potential for interference with the rOCT2.

In contrast, bupropion (0.3-220 μM) and its metabolites (hydroxybupropion [2.74-2000 μM] and threohydrobupropion/erythrohydrobupropion [TB/EB] mixture [1.37-1000 μM]) showed nearly 100% inhibition of the rOCT2 transporter at the highest concentrations tested, which were ~150-750X greater than steady state C_{max} concentrations (Study NB-236). The ratio of the free (unbound) C_{max} and IC₅₀ value was calculated in order to predict clinical relevance of *in vitro* findings; drugs exhibiting ≥ 0.1 C_{max}, free/IC₅₀ ratio presumably exhibit clinical inhibition. Although the C_{max} free/IC₅₀ ratio for bupropion and hydroxybupropion were well below this threshold, the ratio for the TB/EB metabolite mixture was 0.29 suggesting a clinically relevant interaction through inhibition of rOCT2 could occur at therapeutic bupropion doses. Complete reviews of these studies can be found in the clinical pharmacology review.

IC₅₀ Values of the rOCT2 Uptake Inhibition Assay (Sponsor's Table)

TA	Maximal inhibition (%) [*]	IC ₅₀ (μM)
Cimetidine	92.50	83.33
Bupropion	100.00	9.28
Hydroxybupropion	100.00	81.63
TB/EB**	99.78	7.78

* calculated from the equation of the fitted curve at the highest TA concentrations
**TB/EB –mixture of Threohydrobupropion/Erythrohydrobupropion enantiomers

Calculated Parameters from the Drug Total and Free Concentrations in Humans and from IC₅₀ Values (Sponsor's Table)

TA	Dose/day	C _{max, total} (μM) [*]	TA protein binding g (%) ^{**}	C _{max, free} (μM)	C _{max, total} /IC ₅₀ ⁽⁸⁾	C _{max, free} /IC ₅₀
Cimetidine	400 mg ⁽¹⁰⁾	11.8 ⁽¹⁰⁾	25	8.85	0.14	0.11
Bupropion	360 mg	0.667 ⁽¹¹⁾	84	0.107	0.07	0.01
Hydroxybupropion		6.882 ⁽¹¹⁾	84	1.101	0.08	0.01
TB/EB ^{***}		3.917 ⁽¹¹⁾	42	2.272	0.50	0.29

* maximum plasma concentration of TA after steady-state oral administration of 180 mg bupropion SR twice-daily, or 400 mg cimetidine single dose
**binding values of TAs to plasma proteins
***TB/EB –mixture of Threohydrobupropion/Erythrohydrobupropion enantiomers, therefore C_{max} is a sum of two individual C_{max} concentrations (with >80% of total as TB)

6 General Toxicology

No new general toxicology studies were conducted for this 505(b)(2) submission. There have been no nonclinical studies conducted with the combination of naltrexone HCl and bupropion HCl. The approved label for Wellbutrin SR[®] (bupropion HCl), as well as the published literature provided information regarding the target organs of toxicity of naltrexone and bupropion. No-effect dosage levels with adequate margins of safety were identified for each of the adverse treatment-related changes observed with naltrexone. For bupropion, treatment-related, reversible hepatic adverse findings were noted in both the rat and dog at doses that are clinically relevant (mg/m² basis; as low as ~1X MRHD of 360 mg bupropion). The general toxicological profile of naltrexone and bupropion supported the currently approved clinical indications. The known pressor effect of bupropion, which is evident from studies in animals and humans, may contribute more prominently to the risk/benefit profile for the intended obese population which is already at an increased long-term cardiovascular risk compared to the currently approved clinical indications.

Naltrexone

There was no information regarding target organs of toxicity in the approved label for ReVia[®] (naltrexone HCl).

Single dose toxicity of naltrexone was established in the mouse, rat, dog, and monkey (Rosenkrantz, 1984; Braude and Morrison, 1976). Generally, clinical signs of toxicity were similar in all species and by all routes tested. Deaths associated with oral dosing occurred after clonic-tonic convulsions, and were usually preceded by restlessness, tremor, depression, salivation and/or retching and emesis. The LD₅₀ values after oral dosing were 1100-1550 mg/kg

in mice (3300-4650 mg/m²; ~280-390X MHRD of 32 mg naltrexone), 1450 mg/kg in rats (8700 mg/m²; ~740X MHRD of 32 mg naltrexone), and >130 mg/kg in dogs (>2600 mg/m²; >220X MHRD of 32 mg naltrexone). One of four monkeys dosed at 3000 mg/kg (36000 mg/m²; ~3050X MHRD of 32 mg naltrexone) convulsed and died.

There are also published reports of repeat dose toxicity studies (oral and subcutaneous) in the mouse, rat, dog, and monkey (Rosenkrantz, 1984; Braude and Morrison, 1976). Similar to the single dose studies, the target organ/system was the central nervous system. No treatment-related pathology findings were identified. Effects were similar regardless of the route of administration. No adverse effect levels (NOAELs) with adequate margins of safety were established in all species.

Naltrexone General Toxicology (Published Literature): Oral Administration				
Species	Duration	Dose (mg/kg)	NOAEL (32 mg naltrexone/ 19.7 mg/m ²)	Findings
Mouse	90 days (in feed)	0, 30, 100, 3000	3000 mg/kg (~760X MHRD)	No treatment-related findings
Rat	90 days (PO; gavage)	35, 70, 560	70 mg/kg (36X MHRD)	560 mg/kg <ul style="list-style-type: none"> Salivation ↓ weight gain (males) ↑ ketones ↑ ALT (1)
	2 years/ 104 weeks (PO; gavage)	0, 10, 30, 100	10 mg/kg (5X MHRD)	30 and 100 mg/kg <ul style="list-style-type: none"> Hyperirritability (shyness, resistance to handling, vocalization during dosing; dose-related) Alopecia (females only; beginning Wk 14; dose-related)
Dog	13 weeks (PO; capsules)	0, 20, 40, 130→100* *HD group dose reduction after a few days due to tremor, salivation, and emesis.	20 mg/kg (34X MHRD)	20 and 40 mg/kg <ul style="list-style-type: none"> Slight depression (dose-related) 100 mg/kg <ul style="list-style-type: none"> Conditioned salivation, emesis, intermittent slight depression, hind limb stiffness, and tremor; dissipated as study progressed
Monkey	1 year/ 52 weeks (PO; capsules)	0, 6, 12*, 24, 72 *12 mg/kg group added at 3 months	N/A	All doses <ul style="list-style-type: none"> Reaction syndrome (↓ food consumption, weight loss, mucoid rhinitis, hemorrhagic colitis, respiratory infections, and death [2-10 days after initial dose]); possibly due to loss of defense against infection; no histopathological drug-related findings
	1 year (PO; gavage)	0, 1, 5, 10, 20 During the first month of treatment, final doses achieved in a step-wise manner by increasing the dose at weekly intervals from 1→5→10→20 mg/kg.	20 mg/kg (20X MHRD)	Dose-related penile erection during initial weeks.

Bupropion

Single dose toxicity of bupropion was established in the CD1 mouse and Long Evans rat (Tucker, 1983). Generally, clinical signs of toxicity were similar in both species and included ataxia, clonic convulsions, prostration, labored breathing, salivation, arched back, and ptosis. The majority of deaths occurred on the day of dosing (5 minutes to 2 days after oral dosing in mice; 1 to 22 hours after oral dosing in rats). The LD₅₀ values after oral dosing were

544-636 mg/kg in mice (1632-1908 mg/m²; 14-35X MHRD of 360 mg bupropion) and 482-607 mg/kg in rats (2892-3642 mg/m²; 22-27X MHRD of 360 mg bupropion).

Tucker (1983) published a summary of repeat-dose oral toxicity studies in rats (12, 26, and 55 weeks) and the dog (12 and 55 weeks). Treatment-related adverse hepatic findings were observed in both rats and dogs. In subchronic and chronic studies in the rat, there was a dose-related increase in liver weight at ≥ 25 mg/kg (150 mg/m²; ~ 1 X MHRD of 360 mg bupropion). In the rat two-year study, there was an increase in the incidence of hyperplastic nodules (non-neoplastic lesions), heptaocellular hypertrophy, focal hepatocellular hyperplasia, and liver weight at ≥ 100 mg/kg (600 mg/m²; ~ 5 X MHRD of 360 mg/day bupropion). In the chronic dog study (55 weeks), there were reversible histological hepatic findings (centrolobular hepatocellular vacuolation, slight intrahepatic bile duct proliferation, slight centrolobular fibroplasia, and slight Kupffer cell proliferations) and clinical chemistry changes (\uparrow ALT, AST, and ALP) at ≥ 80 mg/kg (1600 mg/m²; ~ 12 X MHRD of 360 mg bupropion), as well as an increase in liver weight at 150 mg/kg (3000 mg/m²; ~ 23 X MHRD of 360 mg bupropion). Histological hepatic findings, increases in liver weight, and clinical chemistry changes (\uparrow ALT, AST, and ALP) in the 55-week dog study were only noted at week 26 in the low dose group (40 mg/kg; 800 mg/m²; ~ 6 X MHRD of 360 mg bupropion). The approved label for Wellbutrin SR[®] describes nonclinical evidence for hepatotoxicity:

In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

At clinically relevant doses (mg/m² basis), dose-related urinary incontinence was observed in rats at all the doses studied (≥ 25 mg/kg; 150 mg/m²; ~ 1 X MHRD of 360 mg bupropion). However, urinary incontinence was not noted in dogs at doses up to 23 times the maximum recommended clinical maintenance dose of bupropion (360 mg; mg/m² basis).

Bupropion General Toxicology (Published Literature): Oral Administration				
Species	Duration	Dose (mg/kg)	NOAEL (360 mg bupropion/ 222 mg/m²)	Findings
Rat	12 weeks (PO; gavage) <i>Long-Evans rats</i>	150, 300, 450 (100, 200, and 300 mg/kg for the 1 st 12 days)	Not established (<150 mg/kg)	<i>All doses</i> <ul style="list-style-type: none"> ▪ Irritability ▪ Urinary incontinence ▪ ↑ liver weight <i>450 mg/kg</i> <ul style="list-style-type: none"> ▪ Death (1)
	26 weeks (PO; gavage) <i>Charles River CD rats</i>	100, 200, 300	Not established	<i>All doses</i> <ul style="list-style-type: none"> ▪ Urinary incontinence ▪ ↑ salivation ▪ Intermittent convulsions (mostly at 300 mg/kg) ▪ ↑ liver weight <i>300 mg/kg</i> <ul style="list-style-type: none"> ▪ Deaths
	55 weeks (PO; gavage) <i>Charles River CD rats</i>	25, 50, 100	Not established (<25 mg/kg)	<i>All doses</i> <ul style="list-style-type: none"> ▪ Urinary incontinence ▪ ↑ salivation ▪ ↑ liver weight <i>100 mg/kg</i> <ul style="list-style-type: none"> ▪ ↑ kidney weight
Dog	12 weeks (PO; gelatin capsules)	15, 30, 75→150 *HD: ↑ from Day 46 onward.	150 mg/kg (23X MHRD)	No treatment-related findings
	52 weeks (PO; gavage)	40, 80, 150	40 mg/kg (6X MHRD)	<i>150 mg/kg</i> <ul style="list-style-type: none"> ▪ Deaths (2) ▪ Salivation (frequent), emesis ▪ Convulsions, weakness, trembling, and ataxia, ▪ ↓ body weight ▪ ↑ kidney and liver weight ▪ Liver histopathology; reversible ▪ ↑ ALT, AST, and ALP; reversible ▪ ↓ Hemoglobin, packed cell volume, and erythrocytes <i>80 mg/kg</i> <ul style="list-style-type: none"> ▪ Deaths (1) ▪ Salivation (occasional) ▪ Emesis ▪ ↑ liver weights (wk 26) ▪ Liver histopathology; reversible ▪ ↑ ALT, AST, and ALP; reversible <i>40 mg/kg</i> <ul style="list-style-type: none"> ▪ ↑ ALT, AST, and ALP (wk 26) ▪ ↑ liver weights (slight; wk 26) ▪ Liver histopathology (wk 26)

7 Genetic Toxicology

No new genetic toxicology studies were conducted for this 505(b)(2) submission. The genotoxicity of naltrexone and bupropion, separately, were previously established in *in vitro* and *in vivo* genotoxicity studies. Summaries of the genotoxicity findings are provided in the labels for ReVia® (naltrexone HCl) and Wellbutrin SR® (bupropion HCl).

Naltrexone

According to the approved label for ReVia® (naltrexone HCl):

There is limited evidence of a weak genotoxic effect of naltrexone in one gene mutation assay in a mammalian cell line, in the *Drosophila* recessive lethal assay, and in non-specific DNA repair tests with *E. coli*. However, no evidence of genotoxic potential was observed in a range of other *in vitro* test, including assays for gene mutation in bacteria, yeast, or in a second mammalian cell line, a chromosomal aberration assay, and an assay for DNA damage in human cells. Naltrexone did not exhibit clastogenicity in an *in vivo* mouse micronucleus assay.

Most of the genotoxicity findings of the *in vitro* and *in vivo* assays with naltrexone were published by Brusick et al. (1978), and are summarized in the table below.

Genotoxicity Findings with Naltrexone

Assay	Test System	Findings
Point Mutation and DNA Repair	Plated Cultures with and without S9 Activation (TA-1535, TA-1537, TA-1538, TA-98, TA-100, WP ₂ uvrA ⁻ Pol A ⁻ /Pol A ⁺ , D4) Naltrexone concentrations tested: 1/8, 1/4, 1/2, and 1.0 of the cellular LD ₅₀	Negative findings with the exception of <i>E. coli</i> PolA ⁻ /PolA ⁺
Point Mutation	Microbial suspensions with and without S9 activation (TA-1535, TA-1537, TA-1538, WP ₂ uvrA ⁻ Pol A ⁻ /Pol A ⁺ , D4)	Negative with the exception of <i>S. typhimurium</i> strain TA-1538 under activation conditions
Point Mutation	<i>Neurospora crassa</i> forward mutation system Naltrexone concentration: 2000 µg/mL	Negative
Unscheduled DNA Synthesis	WI-38 cells Naltrexone concentrations: 0.1, 0.5, 1.0 and 2.0 mg/mL	Initial results at 0.1 and 0.5 mg/mL suggestive of a positive effect; not reproduced in a second test
<i>In Vivo</i> Cytogenetics	Bone marrow cells from rats treated acutely or subchronically with 90, 300 or 900 mg/kg naltrexone (PO)	A few aberrations were observed at low incidence but not significantly increased over control frequencies
Heritable Translocation Assay	Male mice treated with 103, 343 or 1030 mg/kg naltrexone for 7 weeks. Gonadal cells of presumptive semi-sterile F ₁ males were examined for translocations	No evidence of naltrexone-induced translocations

Source: Brusick et al. (1978)

Although a mammalian gene mutation assay, a *Drosophila* recessive lethal assay, and in non-specific DNA repair tests with *E. coli*. are suggestive of treatment-related DNA damage, the mammalian gene mutation assay and the *in vivo* studies of clastogenicity in mice (7-week dosing; up to 1030 mg/kg; 3090 mg/m²; ~260X MHRD of 32 mg naltrexone) and rats (single and 5-day dosing; up to 900 mg/kg; 5400 mg/m²; ~460X MHRD of 32 mg naltrexone) were negative.

Bupropion

According to the label for Wellbutrin SR[®] (bupropion HCl):

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1 of 3 *in vivo* rat bone marrow cytogenetic studies.

In the one *in vivo* cytogenetic study, a slight increase in chromosomal damage was noted after the administration of five consecutive oral doses of 300 mg/kg (1800 mg/m²; ~14X MHRD of 360 mg bupropion) in rats, but not doses of 100 and 200 mg/kg (600-1200 mg/m²; ~5-9X MHRD of 360 mg bupropion) (Tucker, 1983). In a second cytogenetic study, there was no chromosomal damage after single doses of 125, 250, or 500 mg/kg.

8 Carcinogenicity

No new carcinogenicity studies were conducted for this 505(b)(2) submission. The carcinogenicity of naltrexone and bupropion, individually, were each previously established in two rodent species (mouse and rat) as established in the labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl). Only naltrexone in the rat was associated with neoplastic findings (i.e., testicular mesotheliomas and tumors of vascular origin) for which a NOEL was established. The carcinogenicity profile of naltrexone and bupropion supported the currently approved clinical indications and does not raise special concern for the intended obese population.

Naltrexone

According to the label for ReVia[®] (naltrexone HCl):

In a 2-year carcinogenicity study in rats, there were small increases in the number of testicular mesotheliomas in males and tumors of vascular origin in males and females. The incidence of mesothelioma in males given naltrexone at a dietary dose of 100 mg/kg/day (600 mg/m²/day [~50X MHRD of 32 mg/day naltrexone]) was 6% compared with the maximum historical incidence of 4%. The incidence of vascular tumors in males and females given a dietary dose of 100 mg/kg/day (600 mg/m²/day [~50X MHRD of 32 mg/day naltrexone]) was 4%, but only the incidence in females was increased compared to a maximum historical control incidence of 2%. There was no evidence of carcinogenicity in a 2-year dietary study with naltrexone in male and female mice.

The NOEL for testicular mesotheliomas and tumors of vascular origin in the rat is 30 mg/kg (180 mg/m²; ~15X MHRD of 32 mg naltrexone).

Rosenkratz (1984) published the findings of 2-year mouse and rat carcinogenicity studies. In the 2-year mouse bioassay, B6C3F mice (n=50/sex/group) were administered doses of 0, 30, and 100 mg/kg in feed (90-300 mg/m²; ~8-25X MHRD of 32 mg/day naltrexone). The most prevalent neoplasms in all groups (early death plus scheduled sacrifices) included liver tumors, lymphomas, and lung neoplasms. However, there was no indication that the neoplasms were drug- or dose-related. A number of non-neoplastic lesions were recorded, but none of these lesions were considered to be drug-related. In a 2-year rat bioassay, Fischer 344 rats (n=50/sex/group) were administered doses of 0, 30, and 100 mg/kg (180-600 mg/m²; ~15-50X MHRD of 32 mg/day naltrexone) in feed. No relationship to drug or dose in spontaneous deaths over the course of the study was established, although the majority of the early deaths were in drug-treated groups. According to Rosenkratz, statistical analysis could not relate tumor

formation to drug administration in any case of frequent or infrequent neoplasia; the small increases in testicular mesotheliomas and vascular tumors above historical background in rats administered a daily dose 100 mg/kg (~50X MHRD of 32 mg/day naltrexone) described in the label were not addressed. None of the non-neoplastic lesions were considered to be life-threatening, and none could be related unequivocally to administration of naltrexone.

Bupropion

According to the label for Wellbutrin SR[®] (bupropion HCl):

Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 mg/kg/day [1800 mg/m²; ~14X MHRD of 360 mg/day bupropion] and 150 mg/kg/day [450 mg/m²; ~3X MHRD of 360 mg/day bupropion], respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day [600-1800 mg/m²; ~5-14X MHRD of 360 mg/day bupropion]; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Tucker (1983) published the findings of mouse and rat carcinogenicity studies. Charles River CD-1 mice (n=50/sex/group) were orally dosed with 50, 100, and 150 mg/kg (150-450 mg/m²; ~1-3X MHRD of 360 mg/day bupropion) for 96 weeks. Convulsions occurred at ≥100 mg/kg (300 mg/m²; ~2X MHRD of 360 mg/day bupropion). There was no treatment-related effect on tumor incidence. There was a dose-related increase in the incidence of dilated blood vessels in the uterus (uterine venous dilation), which were considered non-neoplastic. However, there was no effect on blood vessels of other organs in mice, or vascular changes in the uterus or other organs of rats or dogs in chronic studies. In Charles River CD(SD)BR rats orally dosed with 100, 200, and 300 mg/kg (600-1800 mg/m²; ~5-14X MHRD of 360 mg/day bupropion) for 104 weeks, dose-related signs of toxicity including intermittent convulsions, salivation, and urinary incontinence, which increased in frequency with time, were noted at all doses. There was a high rate of mortality at 300 mg/kg, which was mainly attributed to convulsions. In addition to the increase in incidences of hyperplastic nodules (non-neoplastic lesions) at ≥100 mg/kg (600 mg/m²; ~5X MHRD of 360 mg/day bupropion) as noted in the label, there were also dose-related increases in liver weight and hepatocellular hypertrophy. A drug-related increase in the incidence of focal hepatocellular hyperplasia was also noted at 100 and 200 mg/kg (600-1200 mg/m²; ~5-9X MHRD of 360 mg/day bupropion). The incidence of hepatocellular carcinomas was random and comparable to the spontaneous background incidence of this neoplasm in Charles River CD rats. Metastases from these tumors were not detected. There was no apparent NOAEL for treatment-related liver findings. However, similar hepatocellular toxicity was not observed in mice.

9 Reproductive and Developmental Toxicology

No new reproductive toxicology studies were conducted for this 505(b)(2) submission. The developmental and reproductive toxicity of naltrexone and bupropion, separately, were previously established. The findings of these studies are provided in the labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl). The proposed Pregnancy Category C labeling for the FDC drug product of naltrexone HCl and bupropion HCl is based on naltrexone's Pregnancy Category C status.

Naltrexone

Naltrexone is classified in Pregnancy Category C based on a series of reproductive toxicity studies in rats and rabbits. According to the labeling information for ReVia[®] (naltrexone HCl):

Naltrexone (100 mg/kg/day; [600 mg/m²; 51X MHRD 32 mg naltrexone]; PO) caused a significant increase in pseudopregnancy in the rat. A decrease in the pregnancy rate of mated female rats also occurred. There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known. The fertility effects of the metabolite 6-β-naltrexol are unknown.

Naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses ≥30 mg/kg/day (180 mg/m²/day; [15X MHRD of 32 mg naltrexone]) and to rabbits at oral doses ≥60 mg/kg/day (720 mg/m²/day; [61X MHRD of 32 mg naltrexone]). There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 200 mg/kg/day [rats, 102X MHRD of 32 mg naltrexone; rabbits, 203X MHRD of 32 mg naltrexone]. Rats do not form appreciable quantities of the major human metabolite, 6-β-naltrexol; therefore, the potential reproductive toxicity of the metabolite in rats is not known.

Bupropion

Bupropion is classified in Pregnancy Category C based on a series of reproductive toxicity studies in rats and rabbits. According to the labeling information for Wellbutrin SR[®] (bupropion HCl):

A fertility study in rats at doses up to 300 mg/kg [1800 mg/m²; ~14X MHRD of 360 mg bupropion] revealed no evidence of impaired fertility.

In studies conducted in rats and rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively (approximately [20] and [14] times the MRHD, respectively, on a mg/m² basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, [~2X MHRD of 360 mg bupropion]) and greater. Decreased fetal weights were seen at 50 mg/kg and greater [600 mg/m²; ~5X MHRD of 360 mg bupropion]. When rats were administered bupropion at oral doses of up to 300 mg/kg/day approximately [14] times the MRHD on a mg/m² basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

A two-generation reproduction and fertility study in Long-Evans rats showed that bupropion up to doses of 300 mg/kg had no direct effect of reproductive performance or fertility at doses up to 300 mg/kg (1800 mg/m²; 14X MHRD of 360 mg bupropion) in the parents or offspring up to and through weaning, despite maternal toxicity (CNS toxicity) at ≥200 mg/kg (1200 mg/m²; 9X MHRD of 360 mg bupropion) (Tucker, 1983). Additionally, there were no effects on survival, growth, fertility, or reproductive parameters in the mated F₁ generation, and no differences between the F₂ offspring descended from drug-treated F₀ rats compared to those descended from control-treated F₀ rats.

11 Integrated Summary and Safety Evaluation

This is a 505(b)(2) application for an extended release fixed dose combination (FDC) drug product of naltrexone HCl and bupropion HCl for the treatment of obesity and weight management. This 505(b)(2) application relies primarily on the Agency findings of the safety and efficacy as reflected in the approved product labels for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl), which are both approved for chronic use. The only nonclinical study conducted in support of this application was an *in vitro* hERG channel study of naltrexone and 6- β -naltrexol as requested by the Agency. The sponsor also submitted relevant published literature on the pharmacology, pharmacokinetics/ADME, and toxicology of naltrexone and bupropion in support of this application. No nonclinical safety pharmacology, ADME/PK, or toxicology studies were conducted with the combination of naltrexone and bupropion. A bridge between the reference listed drugs (ReVia[®] [naltrexone HCl] and Wellbutrin SR[®] [bupropion HCl]) and the FDC drug product of naltrexone HCl and bupropion HCl was established through CMC data in lieu of conducting nonclinical bridging studies.

Pharmacology

Naltrexone is a potent and selective mu opioid antagonist, while bupropion is a moderately weak reuptake inhibitor of DA and NE. The major metabolites of both naltrexone (6- β -naltrexol) and bupropion (hydroxybupropion and threohydrobupropion) also contribute to the pharmacodynamic activity of these two drug substances. Nonclinical studies in the published literature suggest that the combination of naltrexone and bupropion has a synergistic action on two distinct sites of the central nervous system (hypothalamus and the mesolimbic dopamine circuit) that influence energy balance (food intake and energy expenditure).

An evaluation of hERG mediated I_{Kr} current by naltrexone and 6- β -naltrexol was conducted in support of this application. Neither naltrexone (up to 3 μ M; 1 μ g/mL; \sim 330X of the clinical C_{max} [0.003 μ g/mL]) nor 6- β -naltrexol (up to 10 μ M; 3 μ g/mL; \sim 60X of the clinical C_{max} [0.05 μ g/mL]) significantly inhibited hERG mediated I_{Kr} current at concentrations exceeding the human mean peak plasma concentrations after repeat dosing (1-week; 32 mg naltrexone SR/360 mg bupropion SR). Moreover, bupropion (up to 28 μ g/mL; 175X of C_{max} [0.16 μ g/mL]) did not affect G protein-activated inwardly rectifying K^+ channels *in vitro* at concentrations that exceeded human mean peak plasma concentrations of bupropion. These findings are consistent with the lack of QTc changes clinically with naltrexone and bupropion, separately or in combination.

Clinically, the FDC drug product of naltrexone HCl and bupropion HCl causes an increase in blood pressure (\sim 1-3 mm Hg) and heart rate (\sim 1-3 bpm), which have been attributable to bupropion due to its sympathomimetic properties due to inhibition of DA and NE reuptake. Although both the ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl) labels cite several treatment-related clinical cardiovascular/hemodynamic effects, the Wellbutrin SR[®] (bupropion HCl) label also carries a precaution of treatment-related hypertension that can be severe in some cases, requiring acute treatment.

Several nonclinical studies suggest that bupropion causes cardiovascular/hemodynamic effects that may be clinically relevant. Bupropion administered acutely (3-10 mg/kg; 60-200 mg/m²; 0.5-1.5X MHRD of 360 mg bupropion; mg/m² basis) at clinically relevant doses caused transient elevations in pulmonary vascular resistance index and mean pulmonary arterial pressure in dogs (Paganelli et al., 2006a) that may be attributable to stimulation of alpha-adrenoceptors in the pulmonary circulation by DA. In addition to pulmonary pressure changes, a subsequent study (Paganelli et al., 2006b) demonstrated treatment-related increases in system vascular

resistance index (SVRI), heart rate, and mean arterial pressure in dogs following a single intravenous dose of 3 mg/kg (60 mg/m²; 0.5X MHRD of 360 mg bupropion; mg/m² basis). Although the changes were not statistically significant, the findings suggest that bupropion may be capable of producing the hemodynamic changes observed clinically. At doses approximately 2-50 times human mean peak plasma concentrations after repeat dosing (1-week; 32 mg naltrexone SR/360 mg bupropion SR; C_{max}=0.16 µg/mL), bupropion (1-30 µM; 0.3-8 µg/mL) also exerted a dose-related positive inotropic response in human myocardium *in vitro* suggesting that bupropion exerts indirect sympathomimetic activity in human myocardium as a result of catecholamine release. It is noteworthy that the two major metabolites of bupropion (hydroxybupropion and threohydrobupropion), which are pharmacologically active and achieve plasma concentrations higher than that of bupropion, may also be capable of producing a similar positive inotropic response. Although the possibility that naltrexone contributes to the observed increases in blood pressure and heart rate can not be excluded, the available *in vitro* and *in vivo* nonclinical data does not suggest that naltrexone plays a significant role in the clinically observed hemodynamic changes.

In vitro studies using cells over-expressing human rOAT2 (renal uptake transporter responsible for active secretion) were conducted to establish the cause for the increase in mean serum creatinine with naltrexone HCl/bupropion HCl treatment in the Phase 3 studies. The studies suggest that the bupropion component of the naltrexone HCl/bupropion HCl treatment inhibit rOAT2 at clinically relevant doses providing a likely mechanism the increases in serum creatinine observed clinically.

ADME/PK

The nonclinical ADME properties and pharmacokinetics (PK) of naltrexone and bupropion, individually, were previously established. There is no apparent overlap in the pharmacokinetics of the two drugs that necessitated a nonclinical evaluation of the combination. The PK and drug-drug interaction studies conducted under the clinical program adequately established the pharmacokinetics of the drug combination as well as possible drug-drug interactions between naltrexone and bupropion, naltrexone/bupropion tablets and other drugs, and naltrexone and other drugs. The single-dose PK profile of naltrexone HCl/bupropion HCl tablets was highly consistent with that of the approved individual components on a dose-adjusted basis indicating that the PK profile of the drug products are unaltered when administered in combination.

Toxicology

No new toxicology studies were conducted for this 505(b)(2) submission. The potential toxicity unique to the combination of naltrexone and bupropion was not evaluated. However based on the established safety profiles of naltrexone and bupropion, individually, there were no safety concerns regarding significant drug interactions between naltrexone and bupropion in terms of target organ toxicity.

Based on the findings of single and repeat dose toxicity studies in the published literature, naltrexone primarily caused central nervous system (CNS) effects including hyperirritability (30 mg/kg; 180 mg/m²; 15X MHRD of 32 mg naltrexone; mg/m² basis) in rats (2-year study), and salivation, emesis, hind limb stiffness, and tremors (100mg/kg; 2000 mg/m²; 170X MHRD of 32 mg naltrexone; mg/m² basis) in dogs (13-week study). However, there were no pathological findings and no adverse effect levels (NOAELs) with adequate margins of safety were established in all species (mouse, rat, dog, and monkey).

Based on the findings of repeat dose toxicity studies in the rat and dog in the published literature and Wellbutrin SR[®] label, bupropion is associated with hepatotoxicity at doses similar

to or moderately above clinical exposure. The dose-related increases in liver weight in the rat (≥ 25 mg/kg; 150 mg/m²; ~ 1 X MHRD of 360 mg bupropion) that occurred at all dose levels in both subchronic and chronic studies may be related to hepatic enzyme induction. In the two-year rat study, doses of ≥ 100 mg/kg (600 mg/m²; ~ 5 X MHRD of 360 mg/day bupropion) caused hyperplastic nodules (non-neoplastic lesions), hepatocellular hypertrophy, focal hepatocellular hyperplasia, and an increased liver weight; a NOAEL was not established. Similar liver lesions were not seen in the 2-year mouse study. In the 52-week dog study, there were reversible histological hepatic findings (centrilobular hepatocellular vacuolation, slight intrahepatic bile duct proliferation, slight centrilobular fibroplasia, and slight Kupffer cell proliferations) and clinical chemistry changes (\uparrow ALT, AST, and ALP) at ≥ 80 mg/kg (1600 mg/m²; ~ 12 X MHRD of 360 mg bupropion), as well as an increase in liver weight at 150 mg/kg (3000 mg/m²; ~ 23 X MHRD of 360 mg bupropion). Interestingly, at the low dose (40 mg/kg; 800 mg/m²; ~ 6 X MHRD of 360 mg bupropion) in dogs, similar hepatic changes were noted at week 26 but were not present at week 52. There is no *a priori* reason to suspect exacerbation of bupropion-related hepatocellular toxicity when co-administered with naltrexone given the lack of nonclinical data to suggest naltrexone causes hepatocellular toxicity.

Bupropion also elicits seizure activity/convulsions in mice (3 - 4 X MHRD 360 mg bupropion; mg/m² basis) and dogs (2 X MHRD of 360 mg bupropion; mg/m² basis) at doses near clinical exposure, although the mechanism for this remains unresolved. Convulsions caused by naltrexone in the single dose toxicity studies occurred at very large multiples of clinical exposure. Therefore, there is no *a priori* safety concern stemming from the combination of naltrexone and bupropion regarding exacerbation seizure activity caused by bupropion.

The reproductive toxicity, genotoxicity, and carcinogenicity studies described in the approved labeling for ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl) support the chronic administration of the FDC drug product of naltrexone HCl and bupropion HCl.

Both reference listed drug labels carry Pregnancy Category 'C' labeling warranting the recommendation of Pregnancy Category 'C' for the FDC drug product of naltrexone HCl and bupropion HCl. In rabbits, bupropion slightly increased the incidence of fetal malformations and skeletal variations at all doses (≥ 25 mg/kg; 600 mg/m²; ~ 2 X MHRD of 360 mg bupropion; mg/m² basis), as well as decreased fetal weights at 50 mg/kg and greater (600 mg/m²; ~ 5 X MHRD of 360 mg bupropion). However, a retrospective, managed-care database study that assessed exposure to bupropion in the first trimester showed no greater risk for congenital malformations overall or cardiovascular malformations specifically, following first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or bupropion outside of the first trimester. At doses exceeding clinical exposure, naltrexone caused early fetal loss in rats at ≥ 30 mg/kg (180 mg/m²; ~ 15 X MHRD of 32 mg naltrexone) and rabbits at ≥ 60 mg/kg (720 mg/m²; ~ 60 X MHRD of 32 mg naltrexone). Only naltrexone affected fertility in rats causing a significant increase in pseudopregnancy at a dose (100 mg/kg; 600 mg/m²) approximately 50 X the MHRD of naltrexone (32 mg). The potential fertility and reproductive toxicity of 6- β -naltrexol was not established given that rats do not form appreciable quantities of the major human metabolite.

Based on the information in the labels of ReVia[®] (naltrexone HCl) and Wellbutrin SR[®] (bupropion HCl), the carcinogenic potential of naltrexone and bupropion were evaluated in 2-year studies in mice and rats. In the rat, naltrexone was associated with neoplastic findings (i.e., testicular mesotheliomas and tumors of vascular origin) for which a NOEL (30 mg/kg; 180 mg/m²; 15 X MHRD of 32 mg naltrexone) was established. Bupropion caused no drug-related tumors in the rat at doses up to 300 mg/kg (1800 mg/m²; 14 X MHRD of

360 mg/day bupropion) or mouse at doses up to 150 mg/kg (450 mg/m²; 3X MHRD of 360 mg/day bupropion). Overall, the FDC drug product of naltrexone HCl and bupropion HCl poses a minimal carcinogenic risk to humans.

Potentially genotoxic impurities were identified in naltrexone (b) (4) (potential process impurity) and bupropion (b) (4) (chemical intermediate) based on structural alerts. Although the proposed specifications for each impurity will yield a total daily intake of (b) (4) µg, (b) (4), it is reasonable to conclude that the impurities were evaluated in the course of the carcinogenicity and genotoxicity studies described in the reference listed drug labels for naltrexone and bupropion. Therefore, if present at levels above the TTC, nonclinical qualification studies for the impurities are not required.

12 References

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/s/

PATRICIA M BRUNDAGE
12/20/2010

TODD M BOURCIER
12/20/2010
Primary nonclinical review, recommending AP

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 200063 Applicant: Orexigen Therapeutics Stamp Date: 31 March 2010

Drug Name: CONTRAVE NDA/BLA Type: NDA 505(b)2

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		Published reports (nonsearchable, scanned PDF files) visibly clean to read and evaluate.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Literature review of pharmacological, pharmacokinetic, and toxicological properties of Contrave components; includes a written summary of nonclinical information in addition to the sources. Completed hERG evaluation for naltrexone and its primary metabolite 6 β -naltrexol also submitted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		List of excipients provided; excipient review will be conducted.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		Oral dosing was used in the majority of nonclinical studies in the published reports and is the intended route of human exposure.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		A hERG evaluation for naltrexone and its primary metabolite 6 β -naltrexol submitted, as requested.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			Proposed draft labeling was submitted. Information regarding the human dose multiples in mg/m2.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		Limit of NMT ^{(b) (4)} % established for individual specified impurities with the exception of a few potential genotoxic impurities/degradants. Bupropion hydrochloride: ^{(b) (4)} ^{(b) (4)} (NMT ^{(b) (4)} % limit ^{(b) (4)} ppm) and ^{(b) (4)} (NMT ^{(b) (4)} % limit). Naltrexone hydrochloride: ^{(b) (4)} ^{(b) (4)} NMT ^{(b) (4)} % limit).
11	Has the applicant addressed any abuse potential issues in the submission?	X		Assessment of abuse potential submitted.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		n/a	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/

PATRICIA M BRUNDAGE
05/25/2010

TODD M BOURCIER
05/26/2010
NDA fileable for pharm/tox