

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**200063Orig1s000**

**CHEMISTRY REVIEW(S)**



**Memorandum**

**Date:** May 30, 2014  
**From:** Xavier Ysern, PhD, Review Chemist  
**Through:** Danae Christodoulou, PhD, Acting Branch Chief  
**To:** NDA 200-063 Orexigen’s Contrave® Tables  
**Subject:** EES for NDA 200063 Contrave® Tables  
CMC Approval Recommendation

On May 29, 2014 the Office of Compliance issued an “Acceptable” overall recommendation for this NDA into the EES system. There are no pending cGMP inspection issues, see attached report.

The pending CMC issue (see Chemistry Review # 2 dated 17-Dec-2010), response to the Biopharm request on the dissolution specification, has been satisfactorily resolved (see Biopharm’s Review dated 05-May-2014). Besides dissolution specification, there were not CMC changes since 17-Dec-2010.

The CMC recommendation is Approval.

ATTACHED

	<u>Page</u>
Updated Drug Product Specifications (05-May-2014)	2
NDA 200063 EEE Summary Report dated 30-May-2014 (4 pages)	3

**Table P.5.1-1. Contrave Tablets Specifications\* (Update 05-May-2014)**

<i>Attribute</i>	<i>Acceptance Criteria</i>	<i>Method</i>
Appearance	(b) (4) 8 mg/90 mg Blue film coated biconvex tablet, plain on one side and debossed on the other side with "NB-890"	Visual inspection
Bupropion HCl ID (HPLC) <sup>a</sup>	Retention time of peak corresponding to bupropion in the sample conforms to that of the standard.	QUC-TM-00013 or QUC-TM-00004
Naltrexone HCl ID (HPLC) <sup>a</sup>	Retention time of peak corresponding to naltrexone in the sample conforms to that of the standard.	QUC-TM-00013 or QUC-TM-00004
(b) (4)	NMT (b) (4) %	USP (b) (4)
Assay of Naltrexone HCl	(b) (4) % of label claim	QUC-TM-00004
Assay of Bupropion HCl	(b) (4) % of label claim	QUC-TM-00004
Related Substances-Naltrexone HCl <sup>b</sup> Specified: (b) (4)	NMT (b) (4) % NMT % NMT % NMT %	QUC-TM-00004
(b) (4)	NMT %	
Other identified impurities	NMT % each	
Unspecified impurities	NMT % each	
Total (specified + unspecified) impurities	NMT %	
(b) (4)	NMT (b) (4) ppm	
Related Substances-Bupropion HCl <sup>c</sup> Specified: (b) (4)	NMT (b) (4) % NMT % NMT % NMT % NMT % NMT % NMT % NMT %	QUC-TM-00004
USP (b) (4)	NMT %	
USP (b) (4)	NMT %	
(b) (4)	NMT %	
Unspecified impurities	NMT % each	
Total (specified + unspecified)	NMT %	
(b) (4)	NMT (b) (4) ppm	
Uniformity of Dosage Units		QUC-TM-00013
– Naltrexone HCl <sup>a,d</sup>	Conforms to USP <905>	QUC-TM-00013
– Bupropion HCl <sup>a,d</sup>	Conforms to USP <905>	
Dissolution <sup>f</sup> (USP <711>)		QUC-TM-00003
– Naltrexone HCl	0.5 hours: (b) (4) % 1 hour: % 4 hours: NLT (b) (4) %	
– Bupropion HCl	0.5 hour: (b) (4) % 2 hours: (b) (4) % 6 hours: NLT (b) (4) %	
Microbial Limits:		USP <61>/<62>
<i>E. coli</i>	Absent in (b) (4) g	
Total Aerobic Count	NMT (b) (4) cfu/g	
Total Yeasts and Molds	NMT (b) (4) cfu/g	

\* Dissolution specification updates based on Biopharm's review dated 05-May-2014.

<sup>a</sup> Release requirement only.

<sup>b</sup> Any previously unspecified naltrexone impurity routinely observed above the corresponding ICH Q3B(R2) threshold limits will be reported, identified or qualified as appropriate.

<sup>c</sup> (b) (4)

<sup>d</sup> Uniformity of dosage units (b) (4)

<sup>e</sup> (b) (4) See comment on section P.5.4.

<sup>f</sup> Apparatus: (b) (4)

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

<b>Application:</b>	NDA 200063/000	<b>Sponsor:</b>	OREXIGEN
<b>Org. Code:</b>	510		3344 NORTH TORREY PINES RD STE 200
<b>Priority:</b>	4		LA JOLLA, CA 92037
<b>Stamp Date:</b>	31-MAR-2010	<b>Brand Name:</b>	CONTRAVE (NALTREXONE HCL AND BUPROPION H)
<b>PDUFA Date:</b>	11-JUN-2014	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	
<b>District Goal:</b>	02-DEC-2010	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	

002; TABLET, EXTENDED RELEASE; BUPROPION HYDROCHLORIDE; 90MG  
 002; TABLET, EXTENDED RELEASE; NALTREXONE HYDROCHLORIDE; 8MG  
 001; TABLET, EXTENDED RELEASE; BUPROPION HYDROCHLORIDE; 90MG  
 001; TABLET, EXTENDED RELEASE; NALTREXONE HYDROCHLORIDE; 4MG

<b>FDA Contacts:</b>	X. YSERN	Prod Qual Reviewer		3017961779
	R. MCKNIGHT	Product Quality PM		3017961765
	M. JAIRATH	Regulatory Project Mgr	(HFD-510)	3017964267
	S. TRAN	Team Leader		3017961764

<b>Overall Recommendation:</b>	ACCEPTABLE	on 29-MAY-2014	by T. SHARP	()	3017963208
	PENDING	on 13-MAR-2014	by EES_PROD		
	PENDING	on 13-MAR-2014	by EES_PROD		
	PENDING	on 13-MAR-2014	by EES_PROD		
	ACCEPTABLE	on 01-NOV-2010	by EES_PROD		

<b>Establishment:</b>	CFN:	FEI:	(b) (4)	
			(b) (4)	
<b>DMF No:</b>		<b>AADA:</b>		
<b>Responsibilities:</b>	FINISHED DOSAGE RELEASE TESTER			
	FINISHED DOSAGE STABILITY TESTER			
<b>Profile:</b>	CONTROL TESTING LABORATORY	<b>OAI Status:</b>	NONE	
<b>Last Milestone:</b>	OC RECOMMENDATION			
<b>Milestone Date:</b>	13-MAR-2014			
<b>Decision:</b>	ACCEPTABLE			
<b>Reason:</b>	BASED ON PROFILE			

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)  
(b) (4)  
**DMF No:** (b) (4) **AADA:**  
**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER  
**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE  
**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 29-MAY-2014  
**Decision:** ACCEPTABLE  
**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)  
(b) (4)  
**DMF No:** (b) (4) **AADA:**  
**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER  
**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE  
**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 24-APR-2014  
**Decision:** ACCEPTABLE  
**Reason:** DISTRICT RECOMMENDATION

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** (b) (4) **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 13-MAR-2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** (b) (4) **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 13-MAR-2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** (b) (4) **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 13-MAR-2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** (b) (4) **AADA:**

**Responsibilities:** FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER

**Profile:** TABLETS, EXTENDED RELEASE **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 26-MAR-2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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/s/  
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XAVIER J YSERN  
05/30/2014

DANAE D CHRISTODOULOU  
06/02/2014

# NDA 200063

## CONTRAVE®

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

#### Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

**Applicant:** Orexigen Therapeutics, Inc.  
**Address:** 3344 N. Torrey Pines Court, Suite 200  
La Jolla, CA 92037

**Indication:** Treatment of obesity and weight management

**Presentation:** CONTRAVE drug product tablets containing either 4 mg or 8 mg of naltrexone HCl and 90 mg of bupropion HCl (4 mg/90 mg tablet and 8 mg/90 mg strength tablets) are to be supplied in bottles of 120 Tablets. The bottle is a tight (b) (4) container as defined in USP.

**Establishments Evaluation Report (EER) Status:** Acceptable

<b>Consults:</b>	EA -	Acceptable
	Statistics -	N/A
	Methods Validation -	Not recommended
	Biopharm-	Unacceptable
	Microbiology -	N/A
	Pharm Toxicology -	Acceptable

**Original Submission:** March 01, 2010

**Re-submissions:** N/A

**Post-Approval CMC Agreements:** None at this time.

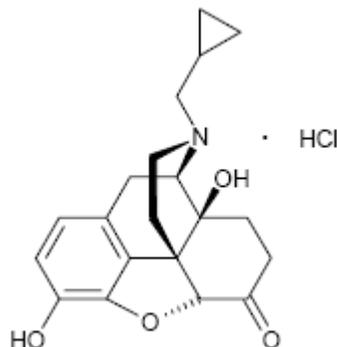
#### Drug Substance Substances:

##### - Naltrexone Hydrochloride

Naltrexone, a substituted oxymorphone, is a potent  $\mu$  (mu) opioid antagonist currently approved for treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. It is marketed as its hydrochloric salt, naltrexone hydrochloride. Naltrexone HCl is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/mL. Naltrexone HCl CMC information is provided in (b) (4) (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4). A (b) (4)

retest date is assigned to drug substance stored at the drug product manufacturing site. Both DMFs were reviewed and found acceptable.

**Chemical name, structural formula, molecular formula and molecular weight**



Molecular Weight: 377.86 daltons

Chemical Formula:  $C_{20}H_{23}NO_4 \cdot HCl$

Chemical Name: Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy, hydrochloride, (5 $\alpha$ ).

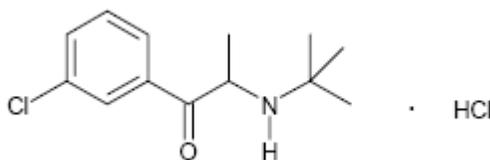
**- Bupropion Hydrochloride**

Bupropion HCl powder is white, crystalline, and highly soluble in water.

(b) (4)

Bupropion HCl CMC information is provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4). Both (b) (4) are the suppliers and manufacturers of the Bupropion HCl employed in the manufacture of the drug product CONTRAVE® (naltrexone HCl and bupropion HCl) Extended-Release Tablet. A (b) (4) retest date is assigned to drug substance stored at the drug product manufacturing site. DMF (b) (4) was reviewed and found acceptable.

**Chemical name, structural formula, molecular formula and molecular weight**



Molecular Weight: 276.2 daltons

Chemical Formula:  $C_{13}H_{18}ClNO_2 \cdot HCl$

Chemical Name: 1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride

**Conclusion:** Drug substances are adequate.

**Drug Product:**

The drug product manufacturing process include a (b) (4)



In addition to the active ingredients, excipients used in the manufacturing process of the drug product include L-cysteine Hydrochloride, Microcrystalline Cellulose, Hydroxypropyl Cellulose, Magnesium Stearate., Lactose Anhydrous, Crospovidone, Edetate Disodium, Colloidal Silicon Dioxide, and Colorants. All excipient meet compendial requirements.

Drug product specifications include Appearance (visual), Identification and Assay for both bupropion and naltrexone, (b) (4) uniformity, Dissolution, Uniformity of Dosage Units (USP<905>), Microbial limits (USP<61/62>), and Purity (HPLC). Based on the stability test data, an expiry dating of 12 months is granted for the drug product.

**Conclusion:** Drug product is not adequate due to the outstanding biopharmaceutical issues outlined in the biopharmaceutical review dated December 21, 2010.

**Overall Conclusion:** The NDA is approvable **pending** a satisfactory Biopharmaceutical review conclusion.

Ali Al-Hakim, Ph.D.  
Branch Chief, Division III  
ONDQA/CDRR/FDA

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/s/  
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ALI H AL HAKIM  
01/04/2011

**NDA 200-063**

**CONTRAVE®**

(naltrexone HCl and bupropion HCl) Extended-Release Tablets  
4 mg/90 mg and 8 mg/90 mg

**Orexigen Therapeutics Inc.**

**Xavier Ysern, PhD**  
**Office of New Drug Quality Assurance**

**Division of Metabolism and Endocrine Products**

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**Chemistry Review Data Sheet**

1. NDA : 200-063  
2. REVIEW #: 2  
3. REVIEW DATE: 17-Dec-2010  
4. REVIEWER: Xavier Ysem, PhD  
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	1-Mar-2010
Amendments:	
0001	04-May-2010 (updated contact information for DS manufacturers)
0002	14-May-2010 (request for proprietary name review)
0005	21-Jun-2010 (package insert)
0007	09-Jul-2010 (response to Day 74 Comments)
0010	29-Jul-2010 (updated 12 month stability data)
0011	26-Aug-2010 (b)(4) content; response to Agency's request dated 02-Aug-2010)

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s)</u>	<u>Document Date</u>
0016	06-Dec-2010 (Response to Agency's request dated 02-Oct-2010)

7. NAME & ADDRESS OF APPLICANT:

Name: Orexigen Therapeutics, Inc.  
Address: 3344 N. Torrey Pines Court, Suite 200  
La Jolla, CA 92037  
Representative: Terry Johnson  
Director Regulatory Affairs  
Telephone: 828 875-8624

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: CONTRAVE®  
b) Non-Proprietary Name (USAN): (naltrexone HCl and bupropion HCl) Extended-Release Tablets  
c) Code Name/# (ONDC only): --  
d) Chem. Type/Submission Priority:  
· Chem. Type: 4  
· Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)  
10. PHARMACOL. CATEGORY: Treatment of obesity and weight management  
11. DOSAGE FORM: Tablet  
12. STRENGTH/POTENCY: 4 mg/90 mg and 8 mg/90 mg (naltrexene/bupropion)

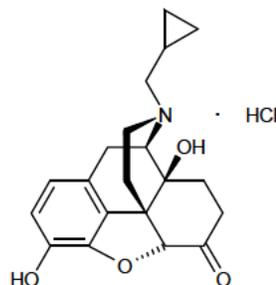
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Naltrexone hydrochloride**

C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub>·HCl

MW: 377.86

CAS RN: 16676-29-2



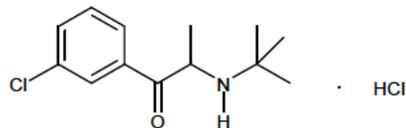
Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy, hydrochloride, (5α)-

**Buprenorphine hydrochloride**

C<sub>13</sub>H<sub>18</sub>ClNO·HCl (C<sub>13</sub>H<sub>19</sub>Cl<sub>2</sub>NO)

MW: 276.2

CAS Registry number: 31677-93-7



1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (1:1)

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	Holder	Item Referenced	Code <sup>1</sup>	Status <sup>2</sup>	Date Review Completed	Comments
Type II (b) (4)	(b) (4)	(b) (4)	1 1 1 1	Adequate Adequate Adequate Adequate	14-Dec-2010 14-Dec-2010 11-Oct-2010 16-Dec-2010	CMC Review # 20 CMC Review # 4 CMC Review # 19 CMC Review # 3
Type IV (b) (4)	(b) (4)	(b) (4)	4 4	Adequate Adequate		LOA 23-Oct-2008 LOA 18-Sep-2009
Type III (b) (4)	(b) (4)	(b) (4)	4 4 4	Adequate Adequate Adequate		LOA 20-Jan-2010 LOA 03-Nov-2009 LOA 03-Nov-2009

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF. 3 – Reviewed previously and no revision since last review.

4 – Sufficient information in application

5 – Authority to reference not granted. 6 – DMF not available.

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

<b>Document</b>	<b>Application #</b>	<b>Description</b>
NDA	20-358	Wellbutrin SR® ((bupropion hydrochloride) Sustained-Release Tablets <i>LOA 21-Sep-2009</i> )

## 18. STATUS:

<b>CONSULTS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	--		
EES	Acceptable	01Nov2010	District Office
OSE/DDMAC	Trade name Contrave Acceptable (OSE RCM 2010-1081)	07Dec2010	Dr. Richard Abate
Pharm/Tox	--		
Biopharm	Pending (See Dr. Tapash Ghosh Biopharm's Review)		
Labeling	Pending (Multidisciplinary Review)		
Methods Validation	Revalidation by Agency laboratories is not recommended		Part of this review
EA	Acceptable		Part of this review
Microbiology	--		

## The Chemistry Review for NDA 22410

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From the CMC point of view, this application is recommended for approval pending satisfactory response to the Biopharm requests (see Dr. Tapash Ghosh Bopharm's Review). All other pending issues: (1) impurity levels for known impurities (b) (4) and (b) (4) and (b) (4) and (2) evaluation of the manufacturing facilities, have been satisfactorily resolved.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

None

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

The drug product, CONTRAVE®, an extended-release tablet, is indicated for the treatment of obesity and weight management. The active components in CONTRAVE drug product are naltrexone, a potent  $\mu$  (mu) opioid antagonist, and bupropion, a biogenic amine reuptake inhibitor, mainly of dopamine (DA) and norepinephrine (NE). CONTRAVE drug product is provided as tablets containing either 4 mg or 8 mg of naltrexone HCl and 90 mg of bupropion HCl (4 mg/90 mg tablet and 8 mg/90 mg tablet). The tablets are packaged in an opaque white high density polyethylene bottle with a (b) (4) screw cap, an induction seal a 3 gram (b) (4) (b) (4) coil to (b) (4)

**• Drug Substance(s)****Naltrexone Hydrochloride**

Naltrexone, a substituted oxymorphone, is a potent  $\mu$  (mu) opioid antagonist currently approved for treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. It is marketed as its hydrochloric salt, naltrexone hydrochloride. Naltrexone HCl is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/mL.

Naltrexone HCl CMC information is provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4). Both (b) (4) and (b) (4) are the suppliers and manufacturers of the Naltrexone HCl employed in the manufacture of the drug product CONTRAVE® (naltrexone HCl and bupropion HCl) Extended-Release Tablet.

In addition of complying with compendial specifications, both sourced Naltrexone HCl drug substance have stricter requirement for impurities and additional particle size distribution requirement. Due to the proposed dosage of the drug product, and based on Pharm-Tox Review Team considerations, the amount of the potential genotoxic impurity (b) (4) is NMT (b) (4) ppm (b) (4) (%). Naltrexone HCl is a (b) (4) is part of the compendial requirements.

During characterization, a number of (b) (4)

For both sites, the drug substance contact surface for the bulk packaging consists of (b) (4) used by (b) (4) used by (b) (4). The (b) (4) used in the container closure systems conform to the requirements cited in 21 CFR §177.1520.

All stability data are provided in (b) (4) Type II DMF (b) (4) and (b) (4) II DMF (b) (4). Up to 48 months of acceptable long term drug substance stability data, and up to 6 months of acceptable accelerated and 9 months ongoing long term drug substance stability data, are provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4), respectively. A (b) (4) retest date is assigned to drug substance stored at the drug product manufacturing site.

### Bupropion Hydrochloride

Bupropion, a phenyl aminoketone compound, is a norepinephrine and dopamine reuptake inhibitor currently approved for the treatment of major depressive disorder and as an aid to smoking cessation treatment. It is marketed as its hydrochloric salt, bupropion hydrochloride, and manufactured as a racemate designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The activities of the individual (b) (4) (b) (4)

Bupropion HCl CMC information is provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4). Both (b) (4) and (b) (4) are the suppliers and manufacturers of the Bupropion HCl employed in the manufacture of the drug product CONTRAVE® (naltrexone HCl and bupropion HCl) Extended-Release Tablet.

Bupropion HCl powder is white, crystalline, and highly soluble in water. (b) (4) (b) (4)

The drug substance specifications include all requirements of the current USP monograph for bupropion hydrochloride. In addition, the specifications include appearance (visual inspection), residual solvents (USP <467>), and particle size distribution (USP <429>). The amount of the potential genotoxic impurity (b) (4) (b) (4) is NMT (b) (4) ppm (b) (4) (%). Bupropion HCl is a (b) (4) is part of the compendial requirements.

The immediate packaging for the bulk drug substance at each of these sites consists of (b) (4) (b) (4) bags, for which the (b) (4) conform to the requirements pursuant to 21 CFR §177.1520.

All stability data are provided in (b) (4) Type II DMF (b) (4) and (b) (4) II DMF (b) (4). Up to 72 months and 48 months of acceptable long term drug substance stability data are provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4), respectively. A (b) (4) retest date is assigned to drug substance stored at the drug product manufacturing site.

### • Drug Product

#### CONTRAVE® (naltrexone HCl and bupropion HCl) Extended-Release Tablet

CONTRAVE® Extended-Release Tablets are trilayer tablets designed for the oral extended release delivery of the active compounds Naltrexone and Bupropion. CONTRAVE drug product is provided as tablets containing either 4 mg or 8 mg of naltrexone HCl and 90 mg of bupropion HCl (4 mg/90 mg tablet and 8 mg/90 mg strength tablets).

In early stages of formulation the goal was to (b) (4) (b) (4)

(b) (4)

(b) (4)

In addition of Bupropion HCl, the (b) (4) contains L-cysteine Hydrochloride USP (b) (4) Microcrystalline Cellulose (b) (4) NF (b) (4) Hydroxypropyl Cellulose (b) (4) NF (b) (4) and Magnesium Sterarate NF (b) (4). The (b) (4) contains Microcrystalline Cellulose (b) (4) NF (b) (4) Lactose Anhydrous NF (b) (4), Crospovidone (b) (4) NF (b) (4) Magnesium Sterarate NF (b) (4) and a colorant. The (b) (4) contains Naltrexone HCl (active), Microcrystalline Cellulose (b) (4) NF (b) (4), Hydroxypropyl Methylcellulose (b) (4) Hydroxypropyl Cellulose (b) (4) NF (b) (4) Edetate Disodium USP (b) (4) Colloidal Silicon Dioxide NF (b) (4) Magnesium Sterarate NF (b) (4) and Magnesium Sterarate NF (b) (4). The colorants used in the (b) (4) (b) (4) for the 4 mg/90 mg and 8 mg/90 mg strengths (b) (4) and FD&C Blue # 2 Aluminum Lake, respectively. (b) (4) (b) (4) (b) (4) Opadry II Blue (b) (4) for the high strength 8 mg/90 mg. All excipient meet compendial in the case of colorants and coating agents, their components meet compendial requirements.

The drug product manufacture is described as a (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Although the overall weight of the (b) (4) (b) (4) CONTRAVE 8 mg/90 mg, (naltrexone HCl 8 mg/bupropion HCl 90 mg) extended-release tablets, are (b) (4) blue, round, bi-convex, film-coated tablets debossed with "NB-890" on one side. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Drug product specifications include Appearance (visual), Identification and Assay for both bupropion and (b) (4) naltrexone (b) (4)

(b) (4)

Based upon the 24 month real time and the extrapolated data presented herein (statistical analysis), Orexigen proposes an expiration dating period of twelve (12) months for the drug product when stored in the proposed commercial container closure system at 25 °C (77 °F), with excursions permitted from 15-30 °C (59-86 °F). The primary stability studies are ongoing and additional data will be available as it is generated. Since the issue regarding the quantification of the contents of the potential genotoxic impurities (b) (4) (naltrexone related impurity) and (b) (4) (bupropion related impurity) is still unresolved, granting of the expiry date is still pending.

The drug product, CONTRAVE 4 mg/90 mg and 8 mg/ 90 mg, are to be supplied in bottles of 120 Tablets. The product is recommended to be stored at room temperature, "Store at 25 °C (77 °F), excursions permitted to 15 -

30 °C (59 - 86 °F) [see USP Controlled Room Temperature]”, and to be dispensed in a tight, (b) (4) container as defined in USP.

#### **B. Description of How the Drug Product is Intended to be Used**

As described in the package insert, CONTRAVE, a dual pro-opiomelanocortin cell [POMC] enhancer, is indicated for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification. CONTRAVE is recommended for patients with an initial body mass index  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> with one or more risk factors (e.g. diabetes, dyslipidemia, or hypertension).

The recommended daily dose of CONTRAVE is two 8/90 tablets taken twice daily for a total dose of 32 mg naltrexone/360 mg bupropion.

### C. Basis for Approvability or Not-Approval Recommendation

Adequate CMC information has been submitted to allow an evaluation of the quality of both drug substances (b)(4) DMF (b)(4) and (b)(4) DMF (b)(4) for Naltrexone Hydrochloride, and (b)(4) DMF (b)(4) and (b)(4) DMF (b)(4) for Bupropion Hydrochloride) and drug product manufactured, tested and packaged in accordance with the procedures and recommendation given in the original submission and pertinent amendments. All mentioned DMF have been reviewed and currently support NDA 200-063.

As part of the specification of the drug product, the potential genotoxic impurities (b)(4) (b)(4) (a Bupropion HCl related impurity) and (b)(4) (a Naltrexone HCl related impurity) are limited to NMT (b)(4) ppm and NMT (b)(4) ppm, respectively.

NDA 200-036 is **recommended for approval** from the standpoint of chemistry, manufacturing and controls (CMC) **pending** a satisfactory response to the Biopharm requests (see Dr. Tapash Ghosh Biopharm's Review).

### III. Administrative

<b>A. Reviewer's Signature</b>	Xavier Ysem, PhD	Review Chemist/ ONDQA/ ONDQA III/ Branch VII
<b>B. Endorsement Block</b>	Ali Al-Hakim, PhD	Branch Chief/ ONDQA/ ONDQA III/ Branch VII
<b>C. CC Block</b>	Meghna Jairath	Project Manager/ OND/ ODE II/ DMEP

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/s/  
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XAVIER J YSERN  
12/17/2010

ALI H AL HAKIM  
12/17/2010

**NDA 200-063**

**CONTRAVE®**

(naltrexone HCl and bupropion HCl) Extended-Release Tablets  
4 mg/90 mg and 8 mg/90 mg

**Orexigen Therapeutics Inc.**

**Xavier Ysern, PhD**  
**Office of New Drug Quality Assurance**

**Division of Metabolism and Endocrine Products**

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**Chemistry Review Data Sheet**

1. NDA : 200-063  
2. REVIEW #: 1  
3. REVIEW DATE: 28-Oct-2010  
4. REVIEWER: Xavier Ysern, PhD  
5. PREVIOUS DOCUMENTS:

Previous Documents

--

Document Date

--

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s)Document Date

Original

31-Mar-2010

Amendments:

0001

04-May-2010 (updated contact information for DS manufacturers)

0002

14-May-2010 (request for proprietary name review)

0005

21-Jun-2010 (package insert)

0007

09-Jul-2010 (response to Day 74 Comments)

0010

29-Jul-2010 (updated 12 month stability data)

0011

26-Aug-2010 (b)(4) content; response to Agency's request dated 02-Aug-2010)

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Orexigen Therapeutics, Inc.  
Address: 3344 N. Torrey Pines Court, Suite 200  
La Jolla, CA 92037  
Representative: Terry Johnson  
Director Regulatory Affairs  
Telephone: 828 875-8624

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: CONTRAVE®  
b) Non-Proprietary Name (USAN): (naltrexone HCl and bupropion HCl) Extended-Release Tablets  
c) Code Name/# (ONDC only): --  
d) Chem. Type/Submission Priority: · Chem. Type: 4  
· Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of obesity and weight management

11. DOSAGE FORM: Tablet

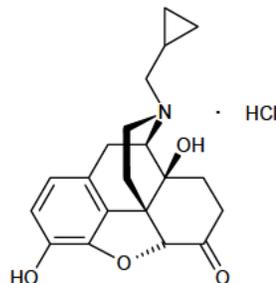
12. STRENGTH/POTENCY: 4 mg/90 mg and 8 mg/90 mg (naltrexone/bupropion)

13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Naltrexone hydrochloride**C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub>·HCl

MW: 377.86

CAS RN: 16676-29-2

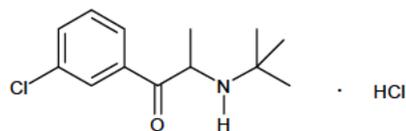


Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy, hydrochloride, (5α)-

**Buprenorphine hydrochloride**C<sub>13</sub>H<sub>18</sub>ClNO·HCl (C<sub>13</sub>H<sub>19</sub>Cl<sub>2</sub>NO)

MW: 276.2

CAS Registry number: 31677-93-7



1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (1:1)

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	Holder	Item Referenced	Code <sup>1</sup>	Status <sup>2</sup>	Date Review Completed	Comments
Type II		(b) (4)	1	Inadequate	05-Oct-2010	CMC Review # 18
			1	Inadequate	17-Sep-2010	CMC Review # 2
			1	Inadequate	21-Sep-2010	CMC Review # 18
			1	Inadequate	17-Sep-2010	CMC Review # 1
Type IV	(b) (4)	(b) (4)	4	Adequate		LOA 23-Oct-2008
			4	Adequate		LOA 18-Sep-2009
Type III	(b) (4)		4	Adequate		LOA 20-Jan-2010
			4	Adequate		LOA 03-Nov-2009
			4	Adequate		LOA 03-Nov-2009

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF. 3 – Reviewed previously and no revision since last review.

4 – Sufficient information in application

5 – Authority to reference not granted. 6 – DMF not available.

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

<b>Document</b>	<b>Application #</b>	<b>Description</b>
NDA	20-358	Wellbutrin SR® ((bupropion hydrochloride) Sustained-Release Tablets <i>LOA 21-Sep-2009</i> )

## 18. STATUS:

<b>CONSULTS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	--		
EES	Pending		
OSE/DDMAC	Proposed trade name Contrave		
Pharm/Tox	--		
Biopharm	Pending		
Labeling	Pending (Multidisciplinary Review)		
Methods Validation	Revalidation by Agency laboratories is not recommended		Part of this review
EA	Acceptable		Part of this review
Microbiology	--		

## The Chemistry Review for NDA 22410

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From the CMC point of view, the application is recommended for approval pending: (1) an acceptable resolution of the deficiencies listed under “Deficiencies and Comments to be Communicated to the Applicant”, (2) an acceptable recommendation for the overall cGMP status of the manufacturing, testing and packaging facilities by the Office of Compliance, (3) satisfactory response to the deficiency letters sent to the DMF holders of DMFs (b) (4) and (4) satisfactory response to Biopharm requests if any (review pending).

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

None

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

The drug product, CONTRAVE®, an extended-release tablet, is indicated for the treatment of obesity and weight management. The active components in CONTRAVE drug product are naltrexone, a potent  $\mu$  (mu) opioid antagonist, and bupropion, a biogenic amine reuptake inhibitor, mainly of dopamine (DA) and norepinephrine (NE). CONTRAVE drug product is provided as tablets containing either 4 mg or 8 mg of naltrexone HCl and 90 mg of bupropion HCl (4 mg/90 mg tablet and 8 mg/90 mg tablet). The tablets are packaged in an opaque white high density polyethylene bottle with a (b) (4) screw cap, an induction seal, a 3 gm (b) (4) (b) (4) coil to (b) (4)

**• Drug Substance(s)****Naltrexone Hydrochloride**

Naltrexone, a substituted oxymorphone, is a potent  $\mu$  (mu) opioid antagonist currently approved for treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. It is marketed as its hydrochloric salt, naltrexone hydrochloride. Naltrexone HCl is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/mL.

Naltrexone HCl CMC information is provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4). Both (b) (4) and (b) (4) are the suppliers and manufacturers of the Naltrexone HCl employed in the manufacture of the drug product CONTRAVE® (naltrexone HCl and bupropion HCl) Extended-Release Tablet.

In addition of complying with compendial specifications, both sourced Naltrexone HCl drug substance have stricter requirement for impurities and additional particle size distribution requirement. Due to the proposed dosage of the drug product, and based on Pharm-Tox Review Team considerations, the amount of the potential genotoxic impurity (b) (4) is requested to be NMT (b) (4) ppm (b) (4) %. Naltrexone HCl is a (b) (4) is part of the compendial requirements.

During characterization, a number of (b) (4) (b) (4)

For both sites, the drug substance contact surface for the bulk packaging consists of (b) (4) (b) (4) used by (b) (4) (b) (4) used by (b) (4). The (b) (4) used in the container closure systems conform to the requirements cited in 21 CFR §177.1520.

All stability data are provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4). Up to 48 months of acceptable long term drug substance stability data, and up to 6 months of acceptable accelerated and 9 months ongoing long term drug substance stability data, are provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4), respectively. A (b) (4) retest date is assigned to drug substance stored at the drug product manufacturing site.

### Bupropion Hydrochloride

Bupropion, a phenyl aminoketone compound, is a norepinephrine and dopamine reuptake inhibitor currently approved for the treatment of major depressive disorder and as an aid to smoking cessation treatment. It is marketed as its hydrochloric salt, bupropion hydrochloride, and manufactured as a racemate designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The activities of the individual (b) (4)

Bupropion HCl CMC information is provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4). Both (b) (4) and (b) (4) are the suppliers and manufacturers of the Bupropion HCl employed in the manufacture of the drug product CONTRAVE® (naltrexone HCl and bupropion HCl) Extended-Release Tablet.

Bupropion HCl powder is white, crystalline, and highly soluble in water. (b) (4)

(b) (4)

The drug substance specifications include all requirements of the current USP monograph for bupropion hydrochloride. In addition, the specifications include appearance (visual inspection), residual solvents (USP <467>), and particle size distribution (USP <429>). Due to the proposed dosage of the drug product, and based on Pharm-Tox Review Team considerations, the amount of the potential genotoxic impurity (b) (4) is requested to be NMT (b) (4) ppm (b) (4) (%). Bupropion HCl is a (b) (4) is part of the compendial requirements.

The immediate packaging for the bulk drug substance at each of these sites consists of (b) (4) (b) (4) bags, for which the (b) (4) conform to the requirements pursuant to 21 CFR §177.1520.

All stability data are provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4). Up to 72 months and 48 months of acceptable long term drug substance stability data are provided in (b) (4) Type II DMF (b) (4) and (b) (4) Type II DMF (b) (4), respectively. A (b) (4) retest date is assigned to drug substance stored at the drug product manufacturing site.

### • Drug Product

#### CONTRAVE® (naltrexone HCl and bupropion HCl) Extended-Release Tablet

CONTRAVE® Extended-Release Tablets are trilayer tablets designed for the oral extended release delivery of the active compounds Naltrexone and Bupropion. CONTRAVE drug product is provided as tablets containing either 4 mg or 8 mg of naltrexone HCl and 90 mg of bupropion HCl (4 mg/90 mg tablet and 8 mg/90 mg strength tablets).

In early stages of formulation the goal was to (b) (4)

(b) (4)

In addition of Bupropion HCl, the (b) (4) contains L-cysteine Hydrochloride USP (b) (4) Microcrystalline Cellulose (b) (4) NF (b) (4), Hydroxypropyl Cellulose (b) (4) NF (b) (4) and Magnesium Sterarate NF (b) (4). The (b) (4) contains Microcrystalline Cellulose (b) (4) NF (b) (4), Lactose Anhydrous NF (b) (4), Crospovidone (b) (4) NF (b) (4), Magnesium Sterarate NF (b) (4) and a colorant. The (b) (4) contains Naltrexone HCl (active), Microcrystalline Cellulose (b) (4) NF (b) (4), Hydroxypropyl Methylcellulose (b) (4) NF (b) (4) Hydroxypropyl Cellulose (b) (4) NF (b) (4) Edetate Disodium USP (b) (4) Colloidal Silicon Dioxide NF (b) (4), Magnesium Sterarate (b) (4) and Magnesium Sterarate (b) (4). The colorants used in the (b) (4) (b) (4) for the 4 mg/90 mg and 8 mg/90 mg strengths are (b) (4) FD&C Blue # 2 (b) (4) Aluminum Lake, respectively. (b) (4) and Opadry II Blue (b) (4) for the high strength 8 mg/90 mg. All excipient meet compendial requirements, or in the case of colorants and coating agents, their components meet compendial requirements.

The drug product manufacture is described as a (b) (4)

Although the overall weight of the (b) (4) (b) (4) CONTRAVE 8 mg/90 mg, (naltrexone HCl 8 mg/bupropion HCl 90 mg) extended-release tablets, are blue, round, bi-convex, film-coated tablets debossed with "NB-890" on one side, (b) (4) (b) (4)

Drug product specifications include Appearance (visual), Identification and Assay for both bupropion and naltrexone (b) (4)

Based upon the 24 month real time and the extrapolated data presented herein (statistical analysis), Orexigen proposes an expiration dating period of twelve (12) months for the drug product when stored in the proposed commercial container closure system at 25 °C (77 °F), with excursions permitted from 15-30 °C (59-86 °F). The primary stability studies are ongoing and additional data will be available as it is generated. Since the issue regarding the quantification of the contents of the potential genotoxic impurities (b) (4) (naltrexone related impurity) and (b) (4) (bupropion related impurity) is still unresolved, granting of the expiry date is still pending.

The drug product, CONTRAVE 4 mg/90 mg and 8 mg/ 90 mg, are to be supplied in bottles of 120 Tablets. The product is recommended to be stored at room temperature, “Store at 25 °C (77 °F), excursions permitted to 15 - 30 °C (59 - 86 °F) [see USP Controlled Room Temperature]”, and to be dispensed in a tight (b) (4) container as defined in USP.

#### **B. Description of How the Drug Product is Intended to be Used**

As described in the package insert, CONTRAVE, a dual pro-opiomelanocortin cell [POMC] enhancer, is indicated for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification. CONTRAVE is recommended for patients with an initial body mass index  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> with one or more risk factors (e.g. diabetes, dyslipidemia, or hypertension).

The recommended daily dose of CONTRAVE is two 8/90 tablets taken twice daily for a total dose of 32 mg naltrexone/360 mg bupropion.

### C. Basis for Approvability or Not-Approval Recommendation

Adequate CMC information has been submitted to allow an evaluation of the quality of both drug substances (b) (4) DMF (b) (4) and (b) (4) DMF (b) (4) for Naltrexone Hydrochloride, and (b) (4) DMF (b) (4) and (b) (4) DMF (b) (4) for Bupropion Hydrochloride) and drug product manufactured, tested and packaged in accordance with the procedures and recommendation given in the original submission and pertinent amendments.

The Sponsor, Orexigen, claims that the potential genotoxic impurity (b) (4) (a Bupropion HCl related impurity) is limited to NMT (b) (4) ppm by the specifications from the suppliers (DMFs (b) (4) and (b) (4)). This asseveration is not supported by the information supplied to the Agency by the DMF holders. The acceptance criterion for the content of the potential genotoxic impurity (b) (4) (b) (4) (a Naltrexone HCl related impurity) is NMT (b) (4) ppm. However, the analytical method described for the determination of Naltrexone Related Substances does not have the sensitivity for a quantitative determination of NMT (b) (4) ppm. These two impurities, which are not degradation products, can be controlled by adequate requirements to both drug substances. However, it is the responsibility of the Sponsor to assure that the drug product meets the criteria for these impurities.

NDA 200-036 is **recommended for approval** from the standpoint of chemistry, manufacturing and controls (CMC) **pending**:

1. an acceptable resolution of the deficiencies listed under "List of Deficiencies to be Communicated",
2. an acceptable recommendation recommendation for the overall cGMP status of the manufacturing, testing and packaging facilities by the Office of Compliance,
3. a satisfactory response to the deficiency letters send to the DMF holders of DMFs (b) (4) (b) (4), and
4. a satisfactory response to Biopharm requests if any (review pending).

### III. Administrative

<b>A. Reviewer's Signature</b>	Xavier Ysern, PhD	Review Chemist/ ONDQA/ ONDQA III/ Branch VII
<b>B. Endorsement Block</b>	Ali Al-Hakim, PhD	Branch Chief/ ONDQA/ ONDQA III/ Branch VII
<b>C. CC Block</b>	Meghna Jairath	Project Manager/ OND/ ODE II/ DMEP

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/s/  
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XAVIER J YSERN  
10/29/2010

ALI H AL HAKIM  
10/29/2010

Initial Quality/CMC Assessment  
ONDQA

**Division of Metabolism and Endocrinology Products**

**NDA:** 200063

**Applicant:** Orexigen Therapeutics Inc.

**Stamp Date:** 31-MAR-2010

**PDUFA Date:** 31-JAN-2011

**Proposed Proprietary Name:** Contrave

**Established Name:** Naltrexone hydrochloride (b) (4)/bupropion  
hydrochloride

**Dosage form and strength:** Extended release tablet  
4 mg/90 mg  
8 mg/90 mg

**Route of Administration:** Oral administration

**Indications:** Treatment of obesity and weight management

**Chemistry classification code** Type 4

**CMC Lead:** Su (Suong) Tran, ONDQA

**ONDQA Fileability:** Yes

Initial Quality/CMC Assessment  
ONDQA

CONSULTS/ CMC RELATED REVIEWS	COMMENT
CBER	<i>Not applicable</i>
CDRH	<i>Not applicable</i>
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
Compliance (DMPQ)	EER was sent to Compliance by ONDQA PM on 26-APR-2010.
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	The product is a solid oral dosage form. Consult may be requested for the review of microbial limits.
OBP	<i>Not applicable</i>
ONDQA Biopharm	Review of biowaivers and all dissolution/drug release-related information. <i>Request was sent to ONDQA Biopharm on 06-APR-2010.</i>
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Pharm/Tox	A consult request will be sent to the PharmTox team for the review of the qualification information on the specified bupropion-related impurities/degradants. The applicant states that qualification information is in the referenced NDA 20358 Wellbutrin SR (different applicant, letter of authorization is provided). Evaluation of impurities for their genotoxic potential.
QbD	<i>Not applicable</i>

This is an electronic NDA, filed as a 505(b)(2) application, with the reference listed drugs (RLD) being Zyban (bupropion hydrochloride), Wellbutrin SR (bupropion hydrochloride), and Aplenzin (bupropion hydrobromide). Note to chemists: the reference to the Zyban and Aplenzin products is for the reliance on FDA's findings of safety and/or effectiveness only, not for any CMC purpose. A letter for the right of reference of NDA 20-358 Wellbutrin SR (bupropion hydrochloride) is provided by GSK, the applicant of Wellbutrin. The letter specifically allows FDA to reference all CMC information in NDA 20358.

Reference is made to the DMF (b) (4) from (b) (4) and DMF (b) (4) from (b) (4) for all CMC information on the bupropion hydrochloride drug substance.

Reference is made to the DMF (b) (4) from (b) (4) and DMF (b) (4) from (b) (4) for all CMC information on the naltrexone hydrochloride drug substance.

## Initial Quality/CMC Assessment ONDQA

Each CONTRAVE tablet is available for oral administration as round, bi-convex, film coated, extended-release tablet. Each tablet has a trilayer core that is composed of two drug layers containing the drug and excipients, and a more rapidly dissolving inert layer separating each drug. Each tablet contains either 4 mg or 8 mg of naltrexone hydrochloride and 90 mg of bupropion hydrochloride. (b) (4)

(b) (4) Tablets containing 8 mg of naltrexone hydrochloride are blue and are debossed with NB-890 on one side. Each tablet contains the following inactive ingredients:

microcrystalline cellulose, hydroxypropyl cellulose, lactose anhydrous, L-cysteine hydrochloride, crospovidone, magnesium stearate, hypromellose, edetate disodium, lactose monohydrate, and colloidal silicon dioxide. In

addition (b) (4) Each 8 mg/90 mg tablet contains Opadry II Blue (b) (4) and dye FD&C Blue #2 aluminum lake.

The product will be packaged in 120-count HDPE bottles with (b) (4) closures and desiccant.

**Maximum daily dose is 32 mg naltrexone HCl (b) (4) and 360 mg bupropion HCl.**

### **Has all information requested during the IND phases, and at the pre-NDA meetings been included?**

The NDA includes some information as requested by FDA during the IND development. There is no item-by-item response to FDA's comments, which makes it difficult to assess in the limited time allotted for this filing memo/IQA whether the applicant has provided a satisfactory response to each question. The primary reviewer will assess the information in the NDA and decide whether issues previously raised have been satisfactorily addressed. The reviewer will also confirm that information previously agreed upon by FDA and the sponsor has not been changed in its final version in the NDA (for example, specifications, packaging systems, etc.)

Major issues discussed in the FDA letter dated 24-MAY-2006 include:

- o Agreement that the primary stability batches will be one (b) (4) batch and two (b) (4) batches. The sponsor was reminded of ICH Q1 guidelines on the selection of batches.

Major issues discussed in the FDA letter dated 07-NOV-2007 include:

- o IVIVC and biowaiver request were not granted based on the available information. The sponsor was told that a BE study will be required if the Phase 3 formulation of the bupropion component is different from the commercial product.

Major issues discussed in the FDA letter in December of 2009 (unclear date) include:

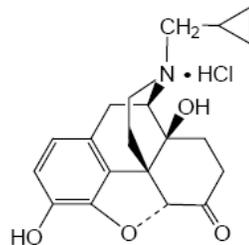
- o Comparability data will be required to qualify commercial drug substance manufacturers.
- o Additional testing will be required in addition to tests in the USP monographs for the 2 drug substances.
- o Treatment of impurities with genotoxic potential.
- o Dissolution data to be included in the NDA.
- o Stability data to be included in the NDA.
- o The sponsor was reminded to submit master production records in support of the 505(b)(2) application and to select an appropriate nomenclature for the dosage form in accordance with FDA's guidelines.

# Initial Quality/CMC Assessment ONDQA

## **Drug substance:**

Naltrexone hydrochloride, USP, 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.

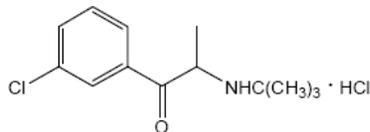
Naltrexone hydrochloride has the chemical name of 17-(cyclopropylmethyl)-4,5 $\alpha$ -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. The empirical formula is C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub>•HCl and the molecular weight is 377.86. The structural formula is:



Naltrexone hydrochloride is a white to yellowish, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/mL.

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Bupropion hydrochloride closely resembles the structure of diethylpropion. It is designated as ( $\pm$ )-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino] propan-1-one hydrochloride. It is related to phenylethylamines. The empirical formula is C<sub>13</sub>H<sub>18</sub>ClNO•HCl and molecular weight is 276.2. The structural formula is:



Bupropion hydrochloride powder is white, crystalline, and highly soluble in water.

## **Review comments:**

Reference is made to the DMF (b) (4) from (b) (4) and DMF (b) (4) from (b) (4) for all CMC information on the bupropion hydrochloride drug substance.

Reference is made to the DMF (b) (4) from (b) (4) and DMF (b) (4) from (b) (4) for all CMC information on the naltrexone hydrochloride drug substance.

- The primary reviewer will review any new information in the DMF submitted after the most recent review.

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- **General properties.** The following information may be critical to the reviewer’s evaluation of manufacturing processes, specifications, product formulations, and stability studies:

- Bupropion: This compound has (b) (4)

(b) (4)

- Naltrexone: (b) (4)

(b) (4)

- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** Comparability data (batch analysis, structural characterization, stability of drug substance and drug product, dissolution profiles of the drug product) are provided to bridge the following changes in drug substance manufacturers:

- Bupropion: Change from (b) (4) (drug substance in clinical product) to (b) (4) (b) (4) and (b) (4) (commercial drug substance).
- Naltrexone: Change from (b) (4) (drug substance in clinical product) to (b) (4) and (b) (4) (commercial drug substance).

The reviewer will evaluate all data to determine whether the commercial product is adequately bridged to the clinical product. It should be noted that (b) (4) has 2 sites in the same city (see 74-day letter comment at the end of this review). No specific biowaiver request is submitted for the commercial product (made with commercial drug substance manufacturers that are different from the clinical product manufacturers). However, the biowaiver request is implied in the dissolution studies conducted to bridge the different drug substance manufacturers. The ONDQA Biopharm reviewer will evaluate the bridging dissolution data.

- **Specifications.** Drug substance specifications are copied on pages 23-24 of this review. The drug substance specifications for both drug substances are based on the USP monographs for these

## Initial Quality/CMC Assessment ONDQA

compounds with additional tests such as description, impurities, residual solvents, and particle size.

- **Impurities.** FDA’s “Guidance for Industry – NDAs: Impurities in Drug Substances” states that ICH Q3A guidelines apply to drug substances that are not new but that are submitted in new NDAs.

- Bupropion: The limit of (b) (4) % is proposed for all specified impurities (except for (b) (4) (b) (4) which meets the ICH qualification threshold. A limit of (b) (4) ppm is proposed for (b) (4) (b) (4) because it is potentially genotoxic. This limit is calculated based on the FDA threshold of 1.5 mcg/day and the maximum daily dose of 360 mg bupropion HCl. The list of impurities (copied on the next pages of this review) will be consulted to the PharmTox team for the evaluation of genotoxic potential.
- Naltrexone: The limit of (b) (4) % is proposed for all specified impurities (except for (b) (4) (b) (4), which meets the ICH qualification threshold. A limit of (b) (4) % is proposed for (b) (4) (b) (4) because it is potentially genotoxic. This limit appears to be (b) (4) the FDA threshold of 1.5 mcg/day given the maximum daily dose of 32 mg naltrexone HCl. The list of impurities (copied on the next pages of this review) will be consulted to the PharmTox team for the evaluation of genotoxic potential.

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

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Structurally Related Compound	Structure	Origin
(b) (4)		

**Drug product**

The composition of the drug product is copied on the next pages.

**Review comments:**

- **Established name and dosage strength.** The proposed established names of the product are “bupropion hydrochloride” and “naltrexone hydrochloride”, which are acceptable because they correlate with the dosage strengths as per current CDER policy on nomenclature. The term (b) (4) may be added to the naltrexone name for clarity.
- **Dosage form.** The product is a fixed dose combination trilayer tablet available in the strengths of 4/90 and 8/90 mg/mg naltrexone hydrochloride (b) (4)/bupropion hydrochloride. The tablet is film-coated with an Opadry II formulation to (b) (4)

- (b) (4)
- (b) (4)
- (b) (4)

- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** The applicant states that (b) (4)% of the phase 3 clinical product (used in studies NB-301, NB-302, NB-303, and NB-304) and all of the primary stability batches were manufactured at the

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commercial (b) (4) site (at (b) (4) scale) with the commercial trilayer tablet formulation, with the (b) (4) Both dosage strengths were used in clinical studies. There is no biowaiver request for any strength.

**Table 3.2.P.1-1 Drug Product Unit Composition (4 mg/tablet Naltrexone Hydrochloride Presentation)**

Ingredient	Nominal Amount			Function
	mg/ tablet	wt% of layer	wt% of tablet <sup>1</sup>	
(b) (4)				

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**Table 3.2.P.1-2 Drug Product Unit Composition (8 mg/tablet Naltrexone Hydrochloride Presentation)**

Ingredient	Amount			Function
	mg/ tablet	wt% of layer	wt% of tablet <sup>1</sup>	
(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)				
(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)				
(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)				
Opadry II Blue (b) (4)				(b) (4)
Overall total:	680		100	(b) (4)

## Manufacturing process of the drug product

The manufacturing process consists of (b) (4)

(b) (4)

(b) (4)

(b) (4)

### Review comments:

## Initial Quality/CMC Assessment ONDQA

- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** The applicant states that (b) (4) % of the phase 3 clinical product (used in studies NB-301, NB-302, NB-303, and NB-304) and all of the primary stability batches were manufactured at the commercial (b) (4) site (at pilot scale, at least (b) (4) % of commercial scale). The commercial batch size will be (b) (4) tablets.
- **Control of critical steps and intermediates.** No quality attribute and no process control are identified as critical. All of the controls are tabulated. The reviewer will identify manufacturing information deemed critical to the product performance for future post-marketing references.
- **Master batch records** are included in the NDA for the commercial manufacturing process (complying with 505(b)(2) regulations).

### Drug product specification

Except for Appearance, all specifications are the same for the different dosage strengths. A representative drug product specification is copied on page 25 of this review.

### Review comments:

- **Limits on degradation products.**
  - Naltrexone: A limit of (b) (4) % is proposed for each specified impurity/degradant, which meets the ICH qualification threshold for the maximum daily dose of 32 mg naltrexone HCl. The reviewer will evaluate all available data and determine if the acceptance criteria for degradants should be expanded. Note: Some of the impurities in the drug product specification are the same as those in the drug substance specification. The list of impurities (copied on the next pages of this review) will be consulted to the PharmTox team for the evaluation of genotoxic potential.
  - Bupropion: The proposed limits (copied below) on all specified impurities/degradants (b) (4) the ICH qualification threshold for the maximum daily dose of 360 mg bupropion HCl. The applicant states that qualification information is in the referenced approved NDA 20358 (different applicant, letter of authorization is provided). The applicant also refers to the limits in the USP monograph, which is not a valid reference per FDA's guidance "NDAs: Impurities in Drug Substances". A consult request will be sent to the PharmTox team for the review of the qualification information on the specified

## Initial Quality/CMC Assessment ONDQA

bupropion-related impurities/degradants. Note: Some of the impurities in the drug product specification are the same as those in the drug substance specification. The list of impurities (copied on the next pages of this review) will be consulted to the PharmTox team for the evaluation of genotoxic potential.

Related Substances – Bupropion Hydrochloride:

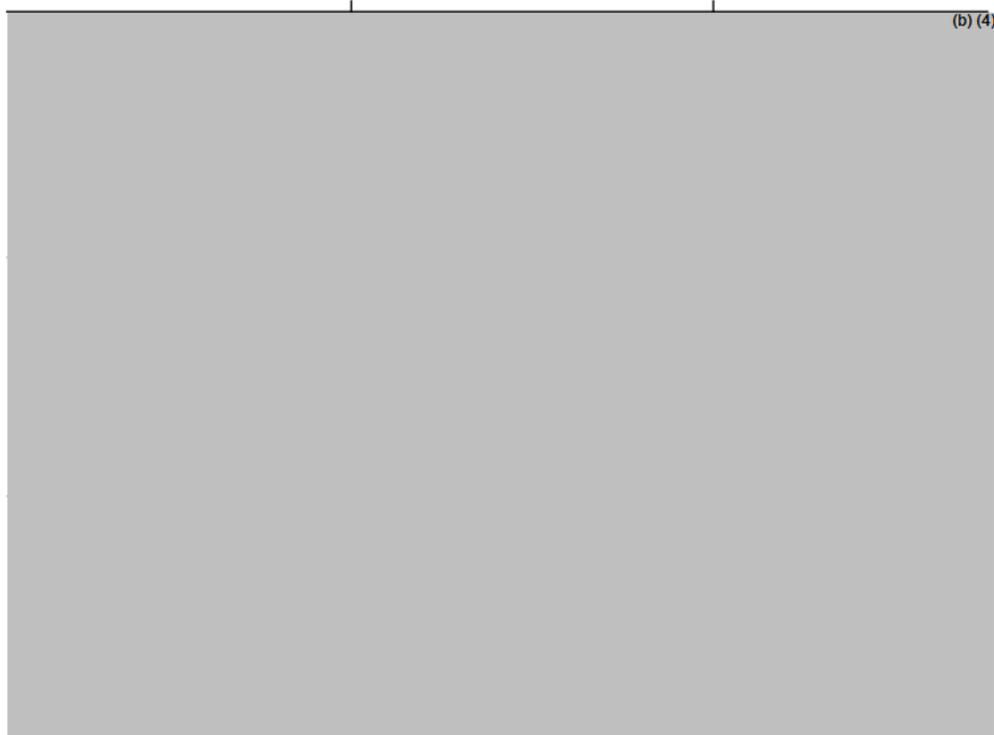
– *Proposed Acceptance Criteria:*

Specified:	(b) (4)	NMT (b) (4) %
		NMT %
		NMT %
		NMT %
		NMT %
		NMT %
		NMT %
		NMT %
Unspecified impurities:		NMT % each
Total (specified + unspecified) impurities:		NMT %

**Table 3.2.P.5.5-1 Overview of Bupropion Hydrochloride Drug Product Degradants**

Structurally Related Compound	Structure	Origin
(b) (4)		

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- **Dissolution.** No specific biowaiver request is submitted for the commercial product made with commercial drug substance manufacturers that are different from the drug substance manufacturers of the clinical product. However, the biowaiver request is implied in the dissolution studies conducted to bridge the different drug substance manufacturers. The ONDQA Biopharm reviewer will evaluate the bridging dissolution data and implied biowaiver request. The applicant states that the dissolution test method is the same as (b) (4) from the USP monograph for Bupropion Hydrochloride Extended Release Tablet. The method is used for both active ingredients. Earlier development work was conducted to optimize the dissolution method using USP Apparatus (b) (4) but there was this work yielded no successful method and the USP method will be used for the commercial product. An alcohol dissolution study was conducted as part of the development work and results are included in the NDA. The dissolution studies, tests, and acceptance criteria will be reviewed by the ONDQA Biopharm team.
- **Microbial limits.** The reviewer may choose to request input from the Microbiology review team on the proposed microbial limits. This drug product is a solid oral dosage form.

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**Container closure systems for product distribution**

The proposed commercial product will be packaged in an opaque white high density polyethylene (HDPE) bottle of nominal (b) (4) capacity with a (b) (4) and a 38 mm (b) (4) screw cap, with an induction seal consisting of (cap surface outwards) white lined (b) (4) foil/ (b) (4) (b) (4) sealable film. This presentation will contain 120 drug product tablets per bottle, along with a nominal 3 gm (b) (4) container and 6 inch (about 12 gm) (b) (4) coil to (b) (4)

**Review comments:**

- **Safety of the packaging components.** The applicant states that all components comply with applicable U.S. indirect food additives regulations 21 CFR 170-199.
- **Suitability of the packaging components.** The applicant states that stability batches were packaged in the proposed commercial container closure systems. In addition, moisture permeation testing was conducted per USP <671>.
- **DMFs.** The primary reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems for solid oral drug products.

**Stability of the drug product**

**Review comments:**

A sufficient amount of stability data is submitted for filing purposes. The applicant states that the primary stability batches have the commercial formulation and were manufactured at the commercial site at a scale at least (b) (4) of the commercial scale, packaged in the proposed commercial container closure systems. In addition, they were manufactured with drug substances from the proposed commercial drug substance manufacturers. The applicant submitted 6-month data for the primary stability batches (at 25 °C/60% RH and 40 °C/75% RH) and requests a shelf life of 12 months at room temperature. The primary batches consist of 3 batches of each dosage strength. The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.

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**Supporting NDA or IND:**

IND 68858: same sponsor

**Supporting DMFs:**

Type II DMFs:

bupropion hydrochloride	(b) (4)	DMF	(b) (4)
bupropion hydrochloride		DMF	
naltrexone hydrochloride		DMF	
naltrexone hydrochloride		DMF	

Component Description	Supplier(s)	Type III DMF Number (b) (4)
[Redacted]		

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Drug Product - CONTRAVE:

The drug product is manufactured, packaged and tested for release by:

Patheon Inc.  
111 Consumers Drive Whitby, Ontario, Canada, L1N 5Z5  
Establishment Registration Number 3003516812

Contact: Brian Dale  
Director of Quality Operations  
Patheon Inc.  
111 Consumers Drive Whitby, Ontario, Canada, L1N 5Z5  
Phone: (905) 430-4206  
Fax: (905) 666-4984  
Email: brian.dale@patheon.com

The drug product is tested for stability, and may also be tested for release, by:

Analytical Bio-Chemistry (ABC) Laboratories, Inc.  
4780 Discovery Drive  
Columbia, MO 65201  
Establishment Registration Number 3007069176

Contact: Kevin Roberson  
Director, GMP Quality Assurance  
ABC Laboratories, Inc.  
4780 Discovery Drive  
Columbia, MO 65201  
Phone: (573) 777-6257  
Fax: (573) 777-6033  
Email: robersonk@abclabs.com

The drug product is released by:

Orexigen Therapeutics, Inc.  
3344 North Torrey Pines Court  
Suite 200  
La Jolla, CA 92037

Contact: Teri Johnson, Director, Regulatory Affairs  
Orexigen Therapeutics, Inc.  
3344 North Torrey Pines Court, Suite 200  
La Jolla, CA 92037  
Phone: (858) 875-8624  
Fax: (858) 430-5975  
E-mail: tjohnson@orexigen.com

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## Initial Quality/CMC Assessment ONDQA

**Table 2.3.S-5 Bupropion Hydrochloride Drug Substance Specification**

Test	Acceptance Criteria	Method*
Appearance	White or almost white powder	Visual inspection
Identification A	IR spectrum corresponds to that of standard similarly prepared	USP monograph
Identification B	HPLC retention time of the major peak in the sample chromatogram corresponds to that of the standard chromatogram	USP monograph
Identification C	Sample is positive for (b) (4)	USP monograph
(b) (4)	NMT (b) (4) %	USP monograph
Assay	(b) (4) %	USP monograph
Related Compounds:		
(b) (4)	NMT (b) (4) %	USP monograph
	NMT %	
Other individual impurities	NMT (b) %	
Total unidentified impurities	NMT (4) %	
Total (all impurities)	NMT %	
(b) (4)	NMT (b) (4) %	Type II DMF methods
	NMT (b) (4) ppm	USP (b) (4)
	NMT (b) (4) ppm	
	NMT (b) (4) ppm	
Particle Size Distribution (d <sub>90</sub> )	NMT (4) μm	USP <429>

\* For methods referenced to the USP monograph or general chapters, methods determined to be equivalent by appropriate validation/comparison may be used.

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**Table 2.3.S-6 Naltrexone Hydrochloride Drug Substance Specification**

Test	Acceptance Criteria	Method*
Description	White to yellowish powder or crystals	Visual inspection
Completeness of Solution	A 650 mg portion dissolves in 10 mL of water to yield a clear solution	Current USP monograph
Identification (IR)	IR spectrum corresponds to that of standard similarly prepared	Current USP monograph
Identification (HPLC)	The HPLC retention time and peak shape of the major peak in the sample chromatogram corresponds to that of the standard chromatogram	HPLC assay Method
Specific Rotation	(b) (4)	Current USP monograph, with measurement at 20°C
(b) (4)	(b) (4) %	Current USP monograph
Assay	(b) (4) %	Current USP monograph
Related Compounds (HPLC): (b) (4)	NMT (b) (4) % NMT (b) (4) % NMT % NMT % NMT % NMT % NMT % NMT % NMT (b) (4) % NMT (b) (4) %	Current USP monograph
• Each unspecified impurity • Sum of impurities (b) (4)	NMT (b) (4) %	Type II DMF method
Water	NMT (b) (4) %	Current USP monograph
Residue on Ignition	NMT (b) (4) %	Current USP monograph
Heavy Metals	NMT (b) (4) ppm	Current USP monograph
Limit of Total Solvents (b) (4)	Sum of (b) (4) %; NMT (b) (4) %	Current USP monograph
(b) (4)	NMT (b) (4) ppm	USP <467>
Particle Size (d <sub>90</sub> )	NMT (b) (4) μm	USP <429>

\* For methods referenced to the USP monograph or general chapters, methods determined to be equivalent by appropriate validation/comparison may be used.

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**CHEMISTRY NDA FILEABILITY CHECKLIST** (See the attached at the end of this review.)

**4-Day Letter Comments**

Note to Reviewers:

The following comments to the Applicant do not include all the critical issues discussed in this IQA/filing review. Issues discussed in this IQA/filing review are for the primary reviewer's consideration and may not necessarily be included in the 74-day letter.

The applicant's response to the 74-day letter comments will be documented and evaluated as part of the primary CMC review.

Your proposed commercial bupropion hydrochloride manufacturer (b) (4) has two facilities with different street addresses. Clarify whether these two facilities are within a contiguous campus and summarize differences, if any, between them. If this is not the case, provide adequate CMC equivalence information to bridge the two facilities.

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**PRODUCT QUALITY**  
**FILING REVIEW FOR NDA (ONDQA)**

NDA Number: 200063

Established/Proper Name:  
Naltrexone hydrochloride  
(b) (4) /bupropion  
hydrochloride

Applicant: Orexigen  
Therapeutics Inc.

Letter Date: 31-MAR-2010

Stamp Date: 31-MAR-2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			

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7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

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9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?			The applicant has been asked to provide this statement.

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Claim of a categorical exclusion per 21 CFR 25.31

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<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?			Reference is made to DMFs.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to DMFs.
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to DMFs.
15.	Does the section contain controls for the DS?			Reference is made to DMFs.
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to DMFs.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

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<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?	x		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

Initial Quality/CMC Assessment  
ONDQA

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?			See Initial Quality/CMC Assessment

Initial Quality/CMC Assessment  
ONDQA

*{See appended electronic signature page}*

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Su (Suong) Tran  
CMC Lead  
Division of Pre-Marketing Assessment #1  
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

*{See appended electronic signature page}*

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Prasad Peri  
Branch Chief  
Division of Pre-Marketing Assessment #1  
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

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

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/s/

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SUONG T TRAN  
05/26/2010

PRASAD PERI  
05/28/2010  
I concur