

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204242Orig1s000

PHARMACOLOGY REVIEW(S)



FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Addiction Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

ADDENDUM TO NDA 204242 PHARMACOLOGY TOXICOLOGY REVIEW

NDA number: 204242
Product: ZUBSOLV sublingual tablets (buprenorphine and naloxone)
Sponsor: Orexo AB

Reviewer name: Elizabeth A. Bolan, Ph.D.
Division name: Division of Anesthesia, Analgesia and Addiction Products
Memo Date: June 27, 2013

This memo serves to correct two typos which appear in the pharmacology/toxicology review for NDA 204242 (May 31, 2013). In the discussion of the impurities of the naloxone drug substance, (b)(4) was incorrectly written as (b)(4). The mistake appears once in the text and once in Table 5. The corrected versions of the text and table are below.

Impurities in the naloxone drug substance

The qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substance for an MDD of < 2 g/day is 0.15% or 1 mg/day intake, whichever is lower. With the exception of (b)(4), the Applicant has set the specifications for impurities in the naloxone drug substance obtained from (b)(4) at or below (b)(4) (Table 5). The specification for (b)(4) (also referred to as (b)(4)) has been set at (b)(4) which exceeds the ICH Q3A(R2) threshold for qualification. However, the (b)(4) specification (b)(4) is within the drug substance specifications of the referenced product and has been deemed acceptable by the Agency. The NLX drug substance also contains (b)(4) an impurity with a structural alert for mutagenicity. The current acceptable threshold for known genotoxic impurities is NMT 1.5 mcg/day. The Applicant has set the specification of (b)(4) at (b)(4). This specification is within the drug substance specification for (b)(4) of the referenced product and has been deemed acceptable by the Agency. The specification of (b)(4) for (b)(4) in the drug substance is acceptable. The specifications for all of the NLX drug substance impurities/degradants are acceptable from a pharmacology/toxicology perspective.

Table 1 Acceptance criteria specifications for the naloxone drug substance

<i>Impurity</i>	<i>Specification</i>	<i>Acceptable?</i>
------------------------	-----------------------------	---------------------------

1 NDA 204242
Zubsolv
Orexo AB

	(b) (4)	NMT	(b) (4) 0%	Yes
		NMT	(b) (4) 0%	Yes
		NMT	(b) (4) 0%	Yes
		NMT	(b) (4) 0%	Yes
		NMT	(b) (4) 0%	Yes
		NMT	(b) (4) 0%	Yes

*structural alert for mutagenicity

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

/s/

ELIZABETH BOLAN
06/27/2013

RICHARD D MELLON
06/27/2013



FDA Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

ADDENDUM TO NDA 204242 PHARMACOLOGY TOXICOLOGY REVIEW

NDA number: 204242
Product: ZUBSOLV sublingual tablets (buprenorphine and naloxone)
Sponsor: Orexo AB

Reviewer name: Elizabeth A. Bolan, Ph.D.
Division name: Division of Anesthesia, Analgesia and Addiction Products
Review completion date: June 6, 2013

This memo serves to document the acceptability, from the pharmacology/toxicology (P/T) perspective, of the updated stability specifications for the drug product that were submitted by the Applicant during the review cycle for NDA 204242. This memo also documents changes to the proposed labeling in the original P/T NDA review (dated May 31, 2013) after further discussions with the Maternal Health Team.

In the original NDA review, P/T recommended approval of NDA 204242 with no post-marketing studies. This memo does not change the original recommendation.

Drug Product Specifications

The Applicant has submitted updated stability specifications for the drug product with additional specifications for individual impurities/degradants derived from the buprenorphine (BUP) and naloxone (NLX) APIs. The Zubsolv product will be manufactured with two strengths. The low and high strength tablets contain 1.4/0.36 mg/mg and 5.1/1.4 mg/mg BUP and NLX, respectively.

The qualification threshold according to the ICH Q3B(R2) guidelines for impurities/degradants in the drug product for a maximum daily dose (MDD) between 10 mg and 100 mg of BUP administered per day is 0.5% or 200 mcg total daily intake (TDI), whichever is lower. The Applicant has set different specifications for the BUP-derived degradants in the low strength and high strength tablets (Table 1). With the exception of (b) (4) in the low strength tablet, all specifications meet the ICH Q3B(R2) threshold for qualification of 0.5%. (b) (4)

The

specifications for the BUP-derived impurities/degradants in the two strengths of the drug product are considered acceptable.

The MDD of the NLX portion of the Zubsolv product is <10 mg/day, therefore the qualification threshold according to the ICH Q3B(R2) guidelines is 1.0% or 50 mcg TDI, whichever is lower. The specifications for the NLX-derived impurities are presented in Table 1 and are considered acceptable.

Table 1. Zubsolv Drug Product Specifications for NDA 204242

<i>Source</i>	<i>Degradant</i>	<i>Tablet Strength</i>	<i>Specification</i>	<i>Acceptable?</i>
Buprenorphine	(b) (4)	low	NMT (b) (4) %	Yes
		high	NMT (b) (4) %	Yes
	(b) (4)	low	NMT (b) (4) %	Yes
		high	NMT (b) (4) %	Yes
	(b) (4)	low	NMT (b) (4) %	Yes
		high	NMT (b) (4) %	Yes
Naloxone	(b) (4)	low	NMT (b) (4) %	Yes
		high		
	(b) (4)	low	NMT (b) (4) %	Yes
		high		

Changes to Labeling

After discussions with the Maternal Health Team (MHT), the Pregnancy section of the product label has been updated. The changes to the version of the label in the P/T review dated May 31, 2013 are below with additions in red text and deletions in strikeout font.

The statement regarding the clinical relevance of the (b) (4) removed from the Risk Summary at the request of the MHT. However, after the description of the increases in neonatal mortality in the Animal Data section, a statement was added to put the findings of decreased pup viability and lactation indices into perspective. This statement was previously in the Nursing Mothers section of the label. Likewise, as per

discussion with the MHT, the term “(b) (4)” was replaced with “embryofetal death” because “embryofetal death” was purported to be the preferred clinical term.

1.1 Pregnancy

Pregnancy Category C.

Risk Summary

There are no adequate and well-controlled studies of ZUBSOLV sublingual tablets or buprenorphine/naloxone in pregnant women. Limited published data on use of buprenorphine, the active ingredient in Zubsolv, in pregnancy, have not shown an increased risk of major malformations. All pregnancies, regardless of drug exposure, have a background risk of 2-4% for major birth defects, and 15-20% for pregnancy loss. Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant doses. Pre- and postnatal development studies in rats demonstrated dystocia, increased neonatal deaths, and developmental delays. (b) (4)

(b) (4) No clear teratogenic effects were seen with a range of doses equivalent to or greater than the human dose. However, in a few studies, some events such as acephalus, omphalocele, and skeletal abnormalities were observed but these findings were not clearly treatment-related. (b) (4) **Embryofetal death** was also observed in both rats and rabbits. (See Animal Data)

Animal Data

...Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human sublingual dose), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human sublingual dose), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human sublingual dose). **An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices.** ...

Reference List

Kobayashi, K., Yamamoto, T., Chiba, K., Tani, M., Shimada, N., Ishizaki, T., and Y. Kuroiwa, 1998. Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. *Drug Metab. Dispos.* 26:8. 818-821.

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

/s/

ELIZABETH BOLAN
06/10/2013

RICHARD D MELLON
06/10/2013

**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: 204242
Supporting document/s: EDR eCTD 0001
Applicant's letter date: Submit date: 9/5/12
CDER stamp date: Received date: 9/6/12
Product: ZUBSOLV™ sublingual tablets (buprenorphine and naloxone)
Indication: Maintenance treatment of opioid dependence
Applicant: Orexo AB
Review Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer: Elizabeth A. Bolan, Ph.D.
Supervisor/Team Leader: R. Daniel Mellon, Ph.D.
Division Director: Bob Rappaport, M.D.
Project Manager: Matthew Sullivan

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 204242 are owned by Orexo AB or are data for which Orexo AB has obtained a written right of reference.

Any information or data necessary for approval of 204242 that Orexo AB 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 reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 204242.

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	5
1.1	INTRODUCTION	5
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	5
1.3	RECOMMENDATIONS	5
2	DRUG INFORMATION	15
	RELEVANT INDs, NDAs, BLAs AND DMFs	16
2.4	COMMENTS ON NOVEL EXCIPIENTS	17
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	17
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	19
2.7	REGULATORY BACKGROUND	19
3	STUDIES SUBMITTED.....	19
4	PHARMACOLOGY.....	20
4.1	PRIMARY PHARMACOLOGY	20
4.2	SECONDARY PHARMACOLOGY	20
4.3	SAFETY PHARMACOLOGY	20
5	PHARMACOKINETICS/ADME/TOXICOKINETICS	20
6	GENERAL TOXICOLOGY.....	20
7	GENETIC TOXICOLOGY	20
8	CARCINOGENICITY	21
9	REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY	21
10	SPECIAL TOXICOLOGY STUDIES.....	21
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	21

Table of Tables

Table 1	Proposed Label for Zubsolv.....	5
Table 2	Relevant INDs, NDAs and DMFs	16
Table 3	Quantitative excipient composition of low and high strength Zubsolv tablets ..	17
Table 4	Acceptance criteria specifications for the buprenorphine drug substance.....	17
Table 5	Acceptance criteria specifications for the naloxone drug substance	18
Table 6	Stability specifications for Zubsolv.....	18

Table of Figures

Figure 1 Structure of buprenorphine hydrochloride	15
Figure 2 Structure of naloxone hydrochloride.....	16

1 Executive Summary

1.1 Introduction

Orexo AB has submitted NDA 204242 for Zubsolv, a sublingual tablet formulation containing buprenorphine hydrochloride (BUP) and naloxone hydrochloride (NLX) in a fixed 4:1 ratio. The product is planned to be available in two strengths of 1.4 mg/0.36 mg and 5.7 mg/1.4 mg BUP/NLX, respectively. The indication sought by the Applicant is maintenance treatment of opioid dependence. The Applicant is submitting NDA 204242 via the 505(b)(2) regulatory pathway with Suboxone Sublingual Tablets (NDA 20733) as the referenced product. The Applicant is relying on the Agency's findings of safety and the pharmacology, pharmacokinetics, and toxicology information in the label of Suboxone. No new nonclinical studies were required for this NDA and no studies were conducted. The excipients in this formulation can be found in higher amounts in products approved for sublingual or buccal use and do not pose any toxicologic concerns. All impurities/degradants in the drug substances and drug product are controlled at acceptable levels. There are no unique nonclinical issues with this product as compared to other sublingual formulations of its individual components, BUP and NLX.

1.2 Brief Discussion of Nonclinical Findings

No new studies were required or submitted for NDA 204242.

1.3 Recommendations

1.3.1 Approvability

The recommendation from pharmacology/toxicology is that NDA 204242 be approved with no post-marketing studies.

1.3.2 Additional Non Clinical Recommendations

There are no nonclinical safety issues unique to this product relevant to clinical use for NDA 204242.

1.3.3 Labeling

The table below contains the draft labeling submitted by the Applicant, the changes proposed by the reviewer and the rationale for the proposed changes. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red (additions) or strikeout font.

Table 1 Proposed Label for Zubsolv

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
INDICATIONS AND USAGE (b) (4) sublingual tablet is	INDICATIONS AND USAGE ZUBSOLV sublingual tablet is a	The trade name ZUBSOLV has been

<p>indicated for:</p> <ul style="list-style-type: none"> the maintenance treatment of opioid dependence. 	<p>partial opioid agonist indicated for:</p> <ul style="list-style-type: none"> the maintenance treatment of opioid dependence. 	<p>used in place of the (b) (4)</p> <p>The Highlights section must include the appropriate FDA Established Pharmacological Class, partial opioid agonist, for buprenorphine.</p>
<p>USE IN SPECIFIC POPULATIONS</p> <p>(b) (4)</p>	<p>USE IN SPECIFIC POPULATIONS</p> <ul style="list-style-type: none"> Pregnancy: Based on animal data, may cause fetal harm. (8.1) 	<p>As per the Maternal Health Team pregnancy labeling initiative, the standard language for a Pregnancy Category C drug was added to the Highlights section. Both buprenorphine and naloxone are Pregnancy Category C.</p>
<p>8.1 Pregnancy Pregnancy Category C. There are no adequate and well-controlled studies of (b) (4) sublingual tablets or buprenorphine/naloxone in pregnant women. (b) (4)</p> <p>(b) (4)</p> <p>Teratogenic Effects: Effects on embryo-fetal</p>	<p>8.1 Pregnancy Pregnancy Category C.</p> <p>Risk Summary There are no adequate and well-controlled studies of (b) (4) ZUBSOLV sublingual tablets or buprenorphine/naloxone in pregnant women. (b) (4)</p> <p>(b) (4)</p> <p>(b) (4) Limited published data on use of</p>	<p>The data in the Pregnancy section are identical to the referenced Suboxone label. The format has been changed to comply with the Pregnancy and Lactation Labeling Rule. To comply with this rule, the <i>Teratogenic and Nonteratogenic Effects</i> headings have been replaced with an <i>Animal Data</i> section. In collaboration with the Maternal Health Team, an overall Risk Summary has also been added.</p>

<p>development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose (b) (4)). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the recommended human daily dose (b) (4)). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the recommended human daily sublingual dose (b) (4)). In the rabbit, increased post-implantation losses occurred at an oral dose of 40</p>	<p>buprenorphine, the active ingredient in ZUBSOLV, in pregnancy, have not shown an increased risk of major malformations. All pregnancies, regardless of drug exposure, have a background risk of 2-4% for major birth defects, and 15-20% for pregnancy loss. Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant doses. Pre- and postnatal development studies in rats demonstrated dystocia, increased neonatal deaths, and developmental delays. (b) (4) No clear teratogenic effects were seen with a range of doses equivalent to or greater than the human dose. However, in a few studies, some events such as acephalus, omphalocele, and skeletal abnormalities were observed but these findings were not clearly treatment-related. (b) (4) ZUBSOLV sublingual tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. <i>Animal Data</i> ZUBSOLV has been shown to have differences in bioavailability compared to other buprenorphine/naloxone-containing sublingual products. The exposure margins listed below</p>	<p>A statement regarding the comparability of exposure margins for Suboxone and Zubsolv has been added. See discussion below this table for details.</p>
--	---	--

<p>mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day. Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human sublingual dose [redacted]), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose [redacted]), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose [redacted]) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose [redacted]). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoracolumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose [redacted]), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day</p>	<p>are based on body surface area comparisons (mg/m^2) to the recommended human sublingual dose of 16 mg buprenorphine via Suboxone, which is equivalent to a human sublingual dose of 11.4 mg buprenorphine via ZUBSOLV.</p> <p>[redacted] (b) (4)</p> <p>Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human [redacted] (b) (4)).</p> <p>[redacted] No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the recommended human daily sublingual dose of [redacted] (b) (4)).</p> <p>Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by</p>	
---	---	--

<p>(estimated exposure was approximately 6 times the recommended human daily sublingual dose of (b) (4) (b) (4)) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of (b) (4) (b) (4)) were not statistically significant.</p> <p>In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the recommended human daily sublingual dose (b) (4) (b) (4)).</p> <p>Non-teratogenic Effects:</p> <p>Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 11.4 mg on a mg/m² basis). Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 11.4 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 11.4 mg on a mg/m² basis), and after SC doses of 0.1 mg/kg/day and up</p>	<p>increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the recommended human daily sublingual dose (b) (4) (b) (4)). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day. Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose (b) (4) (b) (4)), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human (b) (4) (b) (4) sublingual dose (b) (4) (b) (4)), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human (b) (4) (b) (4) sublingual dose (b) (4) (b) (4)) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human (b) (4) (b) (4) sublingual dose (b) (4) (b) (4)). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoracolumbar ribs) were noted in rats</p>	
--	---	--

<p>(approximately 0.06 times the recommended human daily sublingual dose (b) (4)). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of (b) (4)).</p>	<p>after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose (b) (4)), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose (b) (4)) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose (b) (4)) were not statistically significant.</p> <p>In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the recommended human daily sublingual dose of (b) (4)).</p> <p>Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human (b) (4) sublingual dose (b) (4)). Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately</p>	
---	--	--

	<p>0.5 times the recommended human daily sublingual dose- (b) (4) (b) (4)), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose- (b) (4) (b) (4)), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose- (b) (4) (b) (4)). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human (b) (4) (b) (4) sublingual dose- (b) (4) (b) (4)).</p>	
<p>12.1 Mechanism of Action (b) (4) sublingual tablet contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists (b) (4).</p>	<p>12.1 Mechanism of Action (b) (4) ZUBSOLV sublingual tablet contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists (b) (4).</p>	<p>This section is acceptable.</p>
<p>13 NONCLINICAL TOXICOLOGY (b) (4)</p> <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p>	<p>13 NONCLINICAL TOXICOLOGY (b) (4)</p> <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p>	<p>The data in the Nonclinical Toxicology section are identical to the referenced Suboxone label. A statement regarding the comparability of the exposure margins for Suboxone and</p>

<p>Carcinogenicity:</p> <p>A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose of 11.4/2.8 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted.</p> <p>Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human daily sublingual dose of 11.4 mg on a mg/m² basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in</p>	<p>ZUBSOLV has been shown to have differences in bioavailability compared to other buprenorphine/naloxone-containing sublingual products. The exposure margins listed below are based on body surface area comparisons (mg/m²) to the recommended human sublingual dose of 16 mg buprenorphine via Suboxone, which is equivalent to a human sublingual dose of 11.4 mg buprenorphine via ZUBSOLV.</p> <p>Carcinogenicity:</p> <p>A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose of 11.4/2.8 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted.</p> <p>Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human daily sublingual dose- (b) (4)) for 27 months. As in the buprenorphine/naloxone</p>	<p>Zubsolv has been added. See discussion below this table for details.</p>
---	---	---

<p>CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of (b) (4)).</p> <p>Mutagenicity: The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of <i>S. typhimurium</i> and two strains of <i>E. coli</i>. The combination was not clastogenic in an <i>in vitro</i> cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat. Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (<i>S. cerevisiae</i>) for recombinant, gene convertant, or forward mutations; negative in <i>Bacillus subtilis</i> "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets (<i>E. coli</i>) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of ³[H]thymidine, and positive in unscheduled DNA synthesis (UDS)</p>	<p>carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose (b) (4)).</p> <p>Mutagenicity: The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of <i>S. typhimurium</i> and two strains of <i>E. coli</i>. The combination was not clastogenic in an <i>in vitro</i> cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat. Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (<i>S. cerevisiae</i>) for recombinant, gene convertant, or forward mutations; negative in <i>Bacillus subtilis</i> "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets (<i>E. coli</i>) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular</p>	
---	---	--

<p>test using testicular cells from mice.</p> <p>Impairment of Fertility: Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human daily sublingual dose (b) (4)) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose (b) (4)) had no adverse effect on fertility.</p>	<p>tissue from mice, for both in vivo and in vitro incorporation of [³H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.</p> <p>Impairment of Fertility: Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human daily sublingual (b) (4)) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose (b) (4)) had no adverse effect on fertility.</p>	
---	---	--

With sublingual administration in humans, Zubsolv was shown to have higher BA than the referenced Suboxone product. The substitution of the Zubsolv dose in the nonclinical sections of the label which use AUC comparisons is acceptable. However, substituting the Zubsolv dose in sections which use comparisons based on mg/m² would yield inaccurately high exposure margins. Rather than conducting bridging PK studies in the relevant nonclinical species, a statement will be included in the label to put the exposure margins in context. At the PNDA meeting, the Division provided the following wording for the Applicant to consider:

OX219 has been shown to have greater bioavailability compared to other buprenorphine and naloxone-containing sublingual products. The exposure margins are based on doses that yield equivalent systemic exposures and are therefore comparable.

The above wording was included by the Applicant in their proposed labeling for Zubsolv. After further consideration, the statement was revised by the Division to more clearly explain the comparability of the exposure margins between Zubsolv and Suboxone. The revised paragraph outlines the rationale for the comparability between the exposure margins. It states that Zubsolv has higher SL BA than Suboxone and that the exposure

margins in the label, which are based on BSA comparisons, use the 16 mg dose of Suboxone. The systemic exposure of the 11.4 SL dose of Zubsolv is equivalent to the systemic exposure of the 16 mg SL dose of Suboxone, therefore the exposure margins for the two products are comparable. The wording added to the label is below.

ZUBSOLV has been shown to have differences in bioavailability compared to other buprenorphine/naloxone-containing sublingual products. The exposure margins listed below are based on body surface area comparisons (mg/m^2) to the recommended human sublingual dose of 16 mg buprenorphine via Suboxone, which is equivalent to a human sublingual dose of 11.4 mg buprenorphine via ZUBSOLV.

2 Drug Information

Drug: Buprenorphine Hydrochloride

CAS Registry Number: 53152-21-9

Generic Name: Buprenorphine Hydrochloride

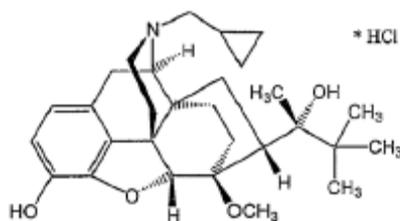
Code Name: BUP/NLX formulation: OX219; accepted trade name: ZUBSOLV

Chemical Name: (2S)-2-[17-(cyclopropylmethyl)-4,5 α -epoxy-3-hydroxy-6-methoxy-6 α ,14-ethano-14 α -morphinan-7 α -yl]-3,3-dimethylbutan-2-ol, hydrochloride

Molecular Formula/Molecular Weight: $\text{C}_{29}\text{H}_{41}\text{NO}_4 \cdot \text{HCl}$; MW= 504.1 g/mol

Structure:

Figure 1 Structure of buprenorphine hydrochloride



Pharmacologic Class: Partial opioid agonist (FDA Established Pharmacologic Class)

Drug: Naloxone hydrochloride

CAS Registry Number: 51481-60-8

Generic Name: Naloxone hydrochloride

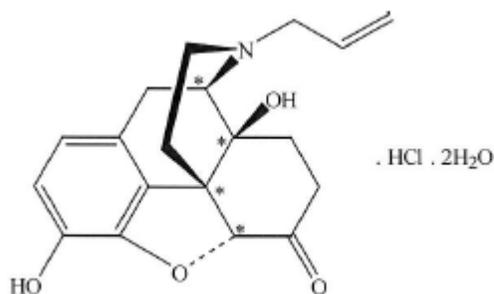
Code Name: BUP/NLX formulation: OX219; accepted trade name: ZUBSOLV

Chemical Name: 4,5 α -Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride

Molecular Formula/Molecular Weight: C₁₉H₂₁NO₄ HCl; MW 399.9 g/mol

Structure:

Figure 2 Structure of naloxone hydrochloride



Pharmacologic class: Opioid antagonist (FDA Established Pharmacologic Class)

Relevant INDs, NDAs, BLAs and DMFs

Table 2 Relevant INDs, NDAs and DMFs

IND/NDA/DMF	Drug/compound	Sponsor	Division/Office	status
IND 110637	OX219	Orexo AB	DAAAP	active
NDA 20733	Suboxone SL tablets (referenced drug)	Reckitt Benckiser	DAAAP	approved
(b) (4)	Buprenorphine HCl	(b) (4)	ONDQA	adequate
	Naloxone HCl		ONDQA	adequate

Drug Formulation

Zubsolv is a sublingual tablet containing buprenorphine hydrochloride and naloxone hydrochloride in a fixed 4 to 1 ratio, respectively. Two strengths are planned to be marketed: 1.4 mg/0.36 mg and 5.7 mg/1.4 mg BUP/NLX. The low strength and high strength tablets utilize (b) (4) formulations as outlined in Table 3. All excipients can be found in drug products approved for sublingual or buccal use at equal or greater levels and therefore do not pose any unique toxicological concerns.

Table 3 Quantitative excipient composition of low and high strength Zubsolv tablets

Excipient	amt per low strength tablet, mg	amt per high strength tablet, mg	Acceptable?
Mannitol		(b) (4)	Yes
Citric acid, (b) (4)			Yes
Sodium citrate (b) (4)			Yes
Microcrystalline cellulose			Yes
Croscarmellose sodium			Yes
Sucralose			Yes
Menthol			Yes
Silicon dioxide, (b) (4)			Yes
Sodium stearyl fumarate			Yes

2.4 Comments on Novel Excipients

Zubsolv does not contain any novel excipients.

2.5 Comments on Impurities/Degradants of Concern

Impurities in the buprenorphine drug substance

The qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substance for a maximum daily dose (MDD) of ≤ 2 g/day is 0.15% or 1 mg/day intake, whichever is lower. The Applicant has set the specifications for impurities in the buprenorphine drug substance obtained from (b) (4) (DMF (b) (4)) at NMT (b) (4) (Table 4) and no qualification will be necessary. The specifications for the buprenorphine drug substance impurities/degradants are acceptable from a pharmacology/toxicology perspective.

Table 4 Acceptance criteria specifications for the buprenorphine drug substance

Impurity	Specification	Acceptable?
(b) (4)	NMT (b) (4) %	Yes
	NMT %	Yes
	NMT %	Yes
	NMT %	Yes
	NMT %	Yes
	NMT %	Yes

Impurities in the naloxone drug substance

The qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substance for an MDD of < 2 g/day is 0.15% or 1 mg/day intake, whichever is lower. With the exception of (b) (4), the Applicant has set the specifications for impurities in the naloxone drug substance obtained from (b) (4) at or below (b) (4) (Table 5). The specification for (b) (4) has been set at (b) (4) which exceeds the ICH Q3A(R2)

threshold for qualification. However, the (b) (4) specification for (b) (4) is within the drug substance specifications of the referenced product and has been deemed acceptable by the Agency. The NLX drug substance also contains (b) (4) (b) (4), an impurity with a structural alert for mutagenicity. The current acceptable threshold for known genotoxic impurities is NMT 1.5 mcg/day. The Applicant has set the specification of (b) (4). This specification is within the drug substance specification for (b) (4) of the referenced product and has been deemed acceptable by the Agency. The specification of (b) (4) for (b) (4) in the drug substance is acceptable. The specifications for all of the NLX drug substance impurities/degradants are acceptable from a pharmacology/toxicology perspective.

Table 5 Acceptance criteria specifications for the naloxone drug substance

<i>Impurity</i>	<i>Specification</i>	<i>Acceptable?</i>
(b) (4)	NMT (b) (4) %	Yes
(b) (4)	NMT (b) (4) %	Yes
(b) (4)	NMT (b) (4) %	Yes
(b) (4)	NMT (b) (4) %	Yes
(b) (4)	NMT (b) (4) %	Yes
(b) (4)	NMT (b) (4) %	Yes

*structural alert for mutagenicity

Impurities in the drug product

The qualification threshold according to the ICH Q3B(R2) guidelines for impurities/degradants in the drug product for an MDD between 10 mg and 100 mg of BUP administered per day is 0.5% or 200 mcg TDI, whichever is lower. The Applicant has set different specifications for the BUP-derived degradant, (b) (4), in the low strength (1.4/0.36 mg/mg BUP/NLX) and high strength (5.1/1.4 mg/mg BUP/NLX) tablets (Table 6). The specification of (b) (4) meets ICH Q3B(R2) thresholds for qualification for the high strength tablet. The specification for the low strength tablet of (b) (4) exceeds ICH Q3B(R2) thresholds for an MDD of 10 to 100 mg. (b) (4) The specifications for the BUP-derived impurity/degradant in the two strengths of the drug product are considered acceptable.

The MDD of the NLX portion of the Zubsolv product is <10 mg/day, therefore the qualification threshold according to the ICH Q3B(R2) guidelines is 1.0% or 50 mcg TDI, whichever is lower. The stability specification for the NLX-derived impurity, (b) (4) in both the low and high strength tablets, is (b) (4). This specification is considered acceptable (Table 6).

Table 6 Stability specifications for Zubsolv

<i>Impurity</i>	<i>Source</i>	<i>Tablet Strength</i>	<i>Specification</i>	<i>Acceptable?</i>
(b) (4)	Buprenorphine:	low	NMT (b) (4) %	Yes

	degradant and API process impurity	high	NMT (b) (4) %	Yes
(b) (4)	Naloxone: degradant and API process impurity	low	NMT %	Yes
		high	NMT %	Yes

2.6 Proposed Clinical Population and Dosing Regimen

The indication sought for Zubsolv is maintenance treatment of opioid dependence. The Applicant plans to market two strengths of Zubsolv sublingual tablets. The systemic exposure of the low strength of Zubsolv, 1.4 mg/0.36 mg BUP/NLX, is equivalent to the Suboxone 2 mg/ 0.5 mg BUP/NLX SL tablet. The high strength of Zubsolv, 5.7 mg/1.4 mg BUP/NLX, is equivalent to the Suboxone 8 mg/2 mg BUP/NLX SL tablet. The product is intended for a single daily dose.

2.7 Regulatory Background

The Applicant submitted NDA 204242 via the 505(b)(2) pathway with Suboxone SL Tablets (NDA 20733) as the referenced product in September of 2012. A PIND meeting (IND 110637) was held with the Applicant in February 2011. The Division communicated to the Applicant that as long as the exposure levels of BUP and NLX are comparable to the referenced product no nonclinical studies for BUP, NLX or the combination appear to be necessary to support a 505(b)(2) application. The Division also provided guidance regarding acceptable levels of impurities, impurities with structural alerts containing α,β -unsaturated ketones and excipients. The issue of increased bioavailability as compared to the referenced product which could lead to possibly misleading exposure margins in the product labeling was also discussed at the PIND meeting. The new IND was submitted in April 2011 and the proposed clinical protocol was allowed to proceed. In June of 2011 the Applicant submitted a meeting request to discuss CMC and nonclinical questions. The Division provided guidance on the specific drug product formulation and impurity issues in writing and the meeting was cancelled. A PreNDA meeting was held in July 2012. Further guidance was provided to the Applicant regarding the appropriate exposure margins for the product labeling. The boilerplate pre-NDA comments were also given to the Applicant.

3 Studies Submitted

No nonclinical studies were required or submitted with NDA 204242.

4 Pharmacology

4.1 Primary Pharmacology

Buprenorphine is a synthetic opioid agonist that is 10-20 times more potent than morphine with a very long duration of action. It acts as a partial mu opioid receptor agonist and a kappa opioid receptor antagonist. Naloxone is a nonspecific opioid receptor antagonist. At low doses BUP produces sufficient agonist effect to enable opioid-addicted individuals to discontinue the misuse of opioids without experiencing withdrawal symptoms. The NLX component of the formulation serves to attempt to prevent abuse of the product. Naloxone is rapidly metabolized via the oral and sublingual routes resulting in low bioavailability, however, with parenteral administration, as in an abuse situation, the NLX is bioavailable to block the effects of BUP and induce withdrawal symptoms in an opioid tolerant person.

4.2 Secondary Pharmacology

The secondary pharmacologic effects of a mu opioid agonist such as BUP include dysphoria, euphoria, and sedation.

4.3 Safety Pharmacology

The CNS effects of BUP are well-known and extensive clinical experience exists with both BUP and NLX. No new safety pharmacology studies were conducted for NDA 204242.

5 Pharmacokinetics/ADME/Toxicokinetics

No new PK studies were submitted for NDA 204242. Based on literature, the major metabolic pathway of BUP in human is via N-dealkylation by CYP3A4 to nor-BUP (Kobayashi K, et al., 1998). The bioavailability of the NLX component of Zubsolv by the sublingual route is very low. The NLX is included in the formulation in order to deter abuse of Zubsolv by parenteral routes.

6 General Toxicology

No general toxicology studies were conducted for NDA 204242.

7 Genetic Toxicology

No genetic toxicology studies were conducted for NDA 204242. Genetic toxicology studies with BUP and the BUP/NLX combination from the label of the referenced product are described in the Zubsolv product label.

8 Carcinogenicity

No carcinogenicity studies were conducted for NDA 204242. Carcinogenicity studies with BUP and the BUP/NLX combination from the label of the referenced product are described in the Zubsolv product label. As discussed in Section 1.3.3 of this review, the sublingual administration of Zubsolv in humans was shown to have higher BA than the referenced Suboxone product. Using the Zubsolv clinical dose for calculating exposure comparisons based on body surface area (in mg/m^2) would yield inaccurately high exposure margins. (b) (4)



9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were conducted for NDA 204242 but studies using BUP and the BUP/NLX combination from the label of the referenced product are described in the Zubsolv product label. Both BUP and NLX are designated Pregnancy Category C. This product will be designated a Pregnancy Category C. As in the carcinogenicity section of the label, some of the comparisons between the clinical dose of Zubsolv and the nonclinical doses in the reproductive toxicology studies are based on body surface area. A statement will be included in the Pregnancy and Nonclinical Toxicology sections of the label to note that although Zubsolv has higher bioavailability than other BUP/NLX products, the systemic exposures and exposure margins are comparable.

10 Special Toxicology Studies

No special toxicology studies were conducted.

11 Integrated Summary and Safety Evaluation

No nonclinical studies were required for NDA 204242. Exposures between Zubsolv and the referenced product Suboxone were shown to be comparable, therefore, no nonclinical studies with either BUP or NLX were deemed necessary. The excipients in this formulation can be found in higher amounts in products approved for sublingual or buccal use and do not pose any toxicologic concerns. All impurities/degradants in the drug substances and drug product are controlled at acceptable levels. The risk assessment of Zubsolv is no different than the referenced product Suboxone.

Reference List

1. Kobayashi K, Yamamoto T, Chiba K, Tani M, Shimada N, Ishizaki T and Kuroiwa Y (1998) Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. *Drug Metab Dispos* **26**:818-821.

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

/s/

ELIZABETH BOLAN

05/31/2013

RICHARD D MELLON

05/31/2013

I concur with Dr. Bolan's recommendation that, from a nonclinical pharmacology toxicology perspective, NDA 204242 may be approved pending agreement with the proposed drug product labeling.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204242 Applicant: Orexo AB

Stamp Date: 9/6/12

**Drug Name: Buprenorphine NDA/BLA Type: 505(b)(2)
and naloxone sublingual
tablets**

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		
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		
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		
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		
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	Not applicable. No studies are required for approval and none were submitted.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

**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/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			Defer to CSS
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

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.

We have no issues for the 74-day letter.

Elizabeth A. Bolan, Ph.D. 11/2/12

 Reviewing Pharmacologist Date

R. Daniel Mellon, Ph.D. 11/2/12

 Team Leader/Supervisor Date

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

/s/

ELIZABETH BOLAN
11/02/2012

RICHARD D MELLON
11/02/2012