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APPLICATION NUMBER:

207932Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 207932
Supporting document/s: DARRTS
Applicant's letter date: December 23, 2014
CDER stamp date: December 23, 2014
Product: BELBUCA™
BioErodable MucoAdhesive (BEMA)
Buprenorphine Hydrochloride Buccal Film
Indication: Management of chronic pain
Applicant: ENDO Pharmaceuticals, Inc.
Review Division: Division of Anesthesia, Analgesia,
and Addiction Products
Reviewer: Gary P. Bond, PhD
Team Leader: Jay H. Chang, PhD
Supervisor: R. Daniel Mellon, PhD
Division Director: Sharon Hertz, MD
Project Manager: Spiros Nicols, PharmD

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1 Executive Summary

1.1 Background and Regulatory Issues

Endo Pharmaceuticals Inc. (Endo) has submitted a New Drug Application (NDA) for Buprenorphine Hydrochloride (HCl) Buccal Film (BELBUCA™) on December 23, 2014 in accordance with 21 CFR 314 and Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The NDA is relying on the Agency's previous determination of safety and efficacy for the listed drugs Buprenex (NDA 18401; approved 12/29/1981) and Subutex (NDA 20732; approved 10/8/2002). Note that Subutex has been discontinued but not for reasons of safety or efficacy according to a Federal Register notice (Docket No. FDA-2013-P-1055; 2/13/2105]. A generic formulation of Subutex was approved under ANDA 78633 (Roxane; 10/8/2009). The Investigational New Drug (IND) application 72428 for Buprenorphine buccal film (BEMA Buprenorphine [BELBUCA™]) was submitted on 12/15/2005 by BioDelivery Sciences International, Inc. (BDSI). The transfer of this IND from BDSI to Endo was made on 12/6/2012.

Buprenorphine HCl is a Schedule III controlled substance with partial agonist properties at μ -opioid receptors and antagonist properties at κ -opioid receptors. Endo and its partner BDSI have developed BELBUCA, a long-acting agent with twice daily dosing. BELBUCA is proposed for the management of chronic pain severe enough to require daily, around-the-clock (ATC), long-term opioid treatment and for which alternative treatment options are inadequate in both opioid-experienced and opioid-naïve populations.

Buprenorphine HCl buccal film uses BDSI's BioErodible MucoAdhesive (BEMA) delivery technology comprised of flexible, water soluble polymeric film which adheres to the moist buccal mucosa and dissolves. Buprenorphine HCl buccal film is designed to enable buccal absorption of buprenorphine, bypassing the gastrointestinal absorption and first pass metabolism processes. The proposed maximum recommended human dose (MRHD) of Belbuca is 900 mcg BID (1.8 mg/day) for opioid experienced and 450 mcg BID for opioid naïve patients. In comparison, the maximum recommended human dose (MRHD) or target dose of Subutex for opioid dependence is 16 mg buprenorphine per day as listed in the Subutex label. The daily maintenance dose is generally in the range of 8 mg to 16 mg buprenorphine per day depending on the individual patient. Therefore, the MRHD for Belbuca is 8.9-fold less of an administered dose of buprenorphine than for Subutex. Note that a relative bioavailability clinical study showed that systemic exposure to buprenorphine after Belbuca administration at the MRHD was within levels for Subutex.

1.2 Brief Discussion of Nonclinical Findings

To support the local and systemic safety of buprenorphine and excipients in the BEMA film, a 28-Day Buccal Toxicity Study of BEMA® Buprenorphine in Beagle Dogs was submitted with this NDA. It was originally submitted by BDSI to support development of BUNAVAIL™ (buprenorphine and naloxone) buccal film under IND 72428 and NDA

205637, which was approved on 6/6/2014. In this study, drug was administered to the same buccal site three times a day for 28 consecutive days. Other than known pharmacological effects of buprenorphine (e.g., abnormal gait and stance, decreased activity, food particle emesis, and excessive salivation, transient weight loss (5-10%) and decreased food consumption), no other buprenorphine-related effects were observed compared to BEMA placebo. The only local toxicity for both groups included minimal to slight cell inflammatory cell infiltration of the oral mucosa. The BEMA buprenorphine disc used in the 28-day dog study was 2.92 cm² and contained 808 mcg buprenorphine/disc (~276 mcg/cm²). The largest Belbuca dose proposed for approval is 2.801 cm² and contains ~900 mcg buprenorphine (321 mcg/cm²) or ~1.2-fold more buprenorphine per cm² than in the nonclinically tested test article. These differences are considered of minimal importance for assessing local toxicity at a 20% difference in concentration with repeated dosing. No issue exists for determining potential systemic toxicity as blood levels will be used to compare animal and human systemic exposure.

While the dogs were dosed three times a day and humans will be dosed up to twice a day, based on these slight concentration differences, the local toxicity of buprenorphine in BEMA buprenorphine cannot be absolutely used to identify and assess potential local toxicity from Belbuca, but is considered an adequate assessment. Therefore, the potential local toxicity of the BEMA film is adequately assessed. What can be noted for the dog dosing is that three repeated doses daily doses to the same buccal dose site did not result in any overt local toxicity. On this basis, the data from the 28-day dog study can be used to assess potential local toxicity and compare systemic exposure of buprenorphine from BEMA buprenorphine to that for Subutex and Belbuca. The dog local tissue toxicity data supports the proposed human dosing with Belbuca.

Review of the composition of the drug substances and drug product along with consultation with ONDQA showed that there are no nonclinical-based safety issues related to impurities, degradants, and excipients.

1.3 Recommendations

1.3.1 Approvability

From the nonclinical perspective, this NDA may be approved. Nonclinical data provide evidence for human safety for the expected systemic exposure to buprenorphine and potential local toxicity from BEMA buprenorphine film.

1.3.2 Additional Non Clinical Recommendations

- none.

1.3.3 Labeling

The table below contains the draft labeling proposed by the Applicant, changes suggested by this reviewer, and the rationale for this reviewer's changes. Note that text to be omitted from the Applicant's proposed draft label is indicated by bold

strikethrough. Text added by this Reviewer or maternal Health Team (MHT) is indicated in underlined bold. The labeling recommendations below have not yet been discussed with the Sponsor and the entire review team. As such, the reader is referred to the action letter for final labeling for this drug product formulation.

Pharm/Tox-related Labeling Sections for NDA 207932 (NOTE: this label may be outdated as numerous changes have been made related to PLLR and ongoing Maternal Health Team PLLR input)		
Label Proposed by Applicant	FDA-Proposed label - adjusted for the PLLR (Pregnancy and Lactation Labeling Rule)	Rationale for Difference
<p align="center">Highlights</p> <p>----INDICATIONS AND USAGE-----</p> <div style="background-color: #cccccc; height: 150px; width: 100%; position: relative;"> (b) (4) </div> <p>----Use in Specific Populations-----</p>	<p align="center">Highlights</p> <p>----INDICATIONS AND USAGE----</p> <p>BELBUCA buccal film <u>contains buprenorphine</u>, a partial opioid agonist. <u>BELBUCA is</u> indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)</p> <p>---Use in Specific Populations---</p> <ul style="list-style-type: none"> • <u>Pregnancy: May cause fetal harm. (8.1)</u> 	<p>Buprenorphine is associated with the reference drug name, not BELBUCA.</p> <p>Attempted consistency with Subutex and other buprenorphine labels adjusted for PLLR but this is final per Maternal Health.</p>
<p>8. Use in Specific Populations</p> <p>8.1. Pregnancy</p> <div style="background-color: #cccccc; height: 100px; width: 100%; position: relative;"> (b) (4) </div>	<p>8. Use in Specific Populations</p> <p>8.1. Pregnancy</p> <p><u>Risk Summary</u></p> <p>There are no adequate and well-controlled studies of BELBUCA or</p>	<p>Use PLLR format. This copy is based on current draft</p>

<p>(b) (4)</p>	<p>buprenorphine in pregnant women. Limited published data on use of buprenorphine, the active ingredient in BELBUCA, in pregnancy, have not shown an increased risk of major malformations. <u>In animal reproduction studies, embryofetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis via the oral route of administration at doses approximately 53 to 11 times the maximum recommended human dose (MRHD), respectively. In pre- and post-natal development studies in rats, dystocia was observed after treatment with buprenorphine via the IM route of administration at a dose approximately 27 times the MRHD, and increased neonatal death was observed after treatment via the oral, IM, and SC routes of administration at doses approximately 4, 3, and 0.5 times the MRHD, respectively. No teratogenic effects were observed in rats treated with buprenorphine via the oral, IM, and IV routes of administration during organogenesis at doses approximately 853, 27, and 4 times the MRHD, respectively, or in rabbits treated with buprenorphine via the oral, SC, and IV routes of administration at doses approximately 267, 53, and 9 times the MRHD, respectively.</u></p>	<p>still under review by review team.</p> <p>All dose ratio calculations based on MRHD of 1.8 mg/day (0.03 mg/kg for 60 kg human) and standard HED conversion factors for animals.</p>
	<p>However, in a few studies,</p>	

	<p><u>some events such as acephalus, omphalocele, and skeletal abnormalities were observed but these findings were not clearly treatment-related.</u> (b) (4)</p> <p>[see Data].</p> <p><u>In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.</u></p> <p><u>Clinical Considerations Fetal/neonatal adverse reactions</u></p> <p>(b) (4)</p> <p>Observe newborns for poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly [see Warnings and Precautions (5.3)].</p> <p><u>Labor or Delivery Opioids cross the placenta and may produce respiratory depression and psychophysiological effects in neonates. An opioid antagonist such as naloxone must be available for reversal of opioid induced respiratory depression in the neonate. BELBUCA is not recommended for use in women immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more</u></p>	<p>Language provided by Maternal Health Team (MHT).</p> <p>Language provided by Maternal Health Team (MHT).</p>
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	<p><u>appropriate. Opioid analgesics, including BELBUCA, can prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor.</u></p> <p>Data</p> <p><i>Animal Data</i></p>	
(b) (4)	<p>Buprenorphine was not teratogenic in rats or rabbits after <u>intramuscular (IM) or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 27 and 53 times, respectively, the maximum human daily buccal BELBUCA dose of 1.8 mg on a mg/m² basis)</u>, after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 4 and 9 times, respectively, the maximum human daily buccal dose of 1.8 mg on a mg/m² basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 853 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 267 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoracolumbar ribs) were noted in rats after SC</p>	

<p>(b) (4)</p>	<p>administration of 1 mg/kg/day and up (estimated exposure was approximately 5 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis), but were not observed at oral doses up to 160 mg/kg/day (estimated exposure was approximately 853 times the MRHD). Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 53 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately 11 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis) were not statistically significant.</p>	
<p>(b) (4)</p>	<p>In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater (estimated exposure was approximately 11 times the MRHD) and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure was approximately 2 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis).</p>	
<p>(b) (4)</p>	<p>Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 27 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis). Fertility, peri- and post-</p>	

<p>(b) (4)</p>	<p>natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 4 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 3 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.5 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis). 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 427 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis).</p>	
<p>13 Nonclinical Toxicology 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>(b) (4)</p> <p><i>Carcinogenesis</i></p>	<p>13 Nonclinical Toxicology 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><i>Carcinogenesis</i></p>	<p>This statement seems to be of limited value since the Applicant's</p> <p>(b) (4)</p>

<p>(b) (4)</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 for 27 months (estimated exposure was approximately 3, 29, and 299 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis). Statistically significant dose-related increases in testicular interstitial (Leydig's) 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 267 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis).</p> <p><u>Mutagenesis</u></p> <p>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.</p> <p>Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study.</p>	<p>(b) (4)</p> <p>Dose ratios slightly different for Applicant's as calculated from actual dose (b) (4)</p>
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(b) (4)	<p>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 <i>in vivo</i> and <i>in vitro</i> incorporation of [³H] thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.</p> <p><u><i>Impairment of Fertility</i></u> Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure approximately 427 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis) or up to 5 mg/kg/day IM or SC (estimated exposure was approximately 27 times the maximum human daily buccal dose of 1.8 mg on a mg/m² basis).</p>	
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2 Drug Information

2.1 Drug

CAS Registry Number

Buprenorphine Hydrochloride: 53152-21-9
Buprenorphine Free Base: 52485-79-7

Generic Name

Buprenorphine Hydrochloride

Code Name

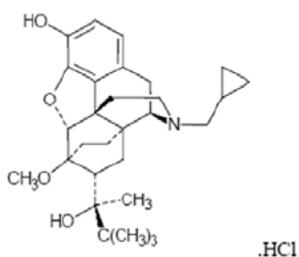
None reported

Chemical Name

6,14-Ethenomorphinan-7-methanol, 17-(cyclopropyl-methyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-, hydrochloride, [5 α ,7 α (S)]

Molecular Formula/Molecular Weight

C₂₉H₄₁NO₄·HCl/ 504.10 (hydrochloride); 467.64 (free base)

Structure**Pharmacologic Class**

Partial Opioid Agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

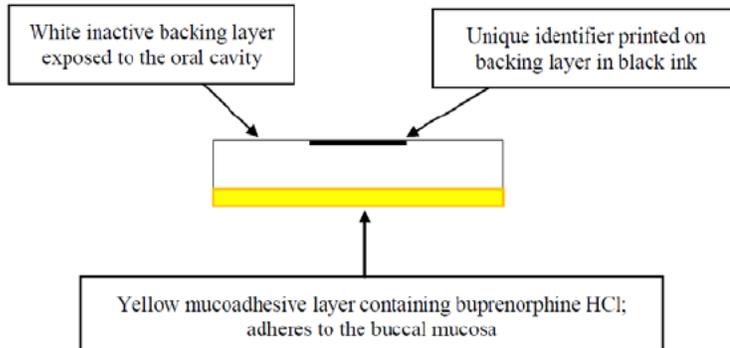
NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
20732	Subutex (buprenorphine HCl)	DAAAP	8 mg (sublingual)	Discontinued	10/8/2002	Opioid dependence and induction	Reckitt Benckiser
18401	Buprenex (buprenorphine HCl)	DAAAP	0.3 mg base/mL (injection)	Prescription	12/29/1981	Moderate to severe pain	Reckitt Benckiser
205637	Bunavail (buprenorphine and naloxone)	DAAAP	6.3/1 mg bases (buccal)	Prescription	6/6/2014	Maintenance treatment of opioid dependence	Biodelivery Science International
22266	BEMA fentanyl (Onsolis)	DAAAP	1.2 mg base buccal film	Discontinued	7/16/2009	Breakthrough pain in patients with cancer	Biodelivery Science International

IND#	Drug	Status	Division	Indication	Stamp Date	Sponsor
72428	BEMA buprenorphine	Active	DAAAP	(b) (4) severe pain	9/10/2007	ENDO Pharmaceuticals Inc.

DMF#	Subject of DMF	Holder	Submit Date	Reviewer's Comment
		(b) (4)	2/18/2014	Adequate
			10/6/2014	Adequate

2.3 Drug Formulation

BELBUCA (buprenorphine hydrochloride) buccal film is available as 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg buprenorphine per film. The films are light yellow to yellow on one side and white to off-white on the other side printed with black ink. The maximum recommended human dose (MRHD) is 900 mcg twice daily (BID).



The White inactive backing layer is exposed to the oral cavity. There is a unique identifier printed on the backing layer in black ink. A yellow mucoadhesive layer containing buprenorphine HCl adheres to the buccal mucosa.

Doses, size, and print marking of the drug product are as follows:

Strength (mcg)	Size (cm ²)	Print Marking
75	1.215	E0
150	2.431	E1
300	0.934	E3
450	1.400	E4
600	1.867	E6
750	2.334	E7
900	2.801	E9

Drug Product Composition (inactive ingredient levels)

(b) (4)

The composition (mg/unit) of

all film strengths is provided in the table.

Following are the adjusted excipient composition levels at the MRHD of 1800 mcg/day buprenorphine (two 900 mcg doses). Based on review of the FDA Inactive Ingredient Database (IID) (public and proprietary) and the FDA Integrity Product Master Data Base, all proposed single-component inactive ingredients are at allowable levels for chronic administration consistent with the review of NDA 205637 (BEMA buprenorphine and naloxone, BUNAVAIL). Though the black Ink (TekPrint™ SW-9008) was not included in BUNAVAIL or tested in the nonclinical studies conducted to support the safety of that formulation, this excipient is listed in the IID as Ink Black SW-9008 with a maximum potency of 0.22 mg for the oral route. The product containing this excipient at this level is approved for chronic use. (b) (4)

(b) (4) in the Belbuca formulation, it is reasonably safe to assume that the trace levels of the black ink in the Belbuca formulation are adequately qualified.

Amount (mg) of Inactive ingredients in Belbuca at MRHD of 900 mcg BID (1800 mcg/day)	
Hydroxypropylcellulose (HPC)	(b) (4) Peppermint Oil (b) (4)
Hydroxyethylcellulose (HEC)	Carboxymethylcellulose Sodium (NaCMC)
Sodium Benzoate	Polycarbophil
Methylparaben	Propylene Glycol
Propylparaben	Yellow Iron Oxide
Citric Acid, Anhydrous	Monobasic Sodium Phosphate, Anhydrous
Vitamin E Acetate	Sodium Hydroxide
Saccharin Sodium	Black Ink (TekPrint™ SW-9008)
Titanium Dioxide	Purified Water

* - assumed to NMT (b) (4) mcg

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance

The combined specifications for buprenorphine hydrochloride by the drug substance manufacturers, (b) (4) and (b) (4) are listed in the table below. Both manufacturers' products are supported by Drug Master File (DMF) (b) (4) and (b) (4) respectively. For additional details, please refer to the DMFs.

The drug substance (DS) specification for individual specified impurities is set at NMT (b) (4) %, which (b) (4) the qualification threshold of NMT 0.15% or 1.0 mg per day intake (whichever is lower) based on the maximum recommended human dose (MRHD)

dose of Belbuca of 1.8 mg buprenorphine/day per the ICH Q3A(R2) guidance. The CMC review team was informed of this issue and the Applicant was informed via an Information Request to (b) (4) the specification based on the very low levels detected in stability studies that showed that all listed impurities were (b) (4)%. The Applicant complied by (b) (4) the specification limit to NMT (b) (4)%, which is acceptable.

The level of the residual solvent (b) (4) specification ((b) (4) ppm – (b) (4)%) is also acceptable even though greater than (b) (4) ppm (b) (4)%) as allowed according to ICH Q3C (Tables and List). This is also not an issue as the actual daily exposure amount for the drug product is (b) (4) ppm which is consistent with ICH Q3C (b) (4) (see second table). ONDQA agrees with this assessment (b) (4)

Specification for Buprenorphine Hydrochloride

Test	Acceptance Criteria	Analytical Method
Appearance	White to almost white powder	Visual
Identification		
Infrared Absorption	Complies with reference spectrum	USP Monograph
Color	(b) (4) color appears immediately	USP Monograph
(b) (4)	Complies	USP Monograph ^a Ph. Eur. Monograph ^b
Specific Rotation	(b) (4)	USP Monograph
pH ^a	(b) (4)	USP Monograph
Acidity or Alkalinity ^b	(b) (4)	Ph. Eur. Monograph
(b) (4)	(b) (4)	USP Monograph
Residue on Ignition	(b) (4)	USP Monograph
(b) (4)	(b) (4)	HPLC
Residual Solvents	(b) (4)	Ph. Eur. Monograph USP<467>
Chromatographic Purity	(b) (4)	
Individual Specified Impurity	(b) (4)	Ph. Eur. Monograph
Individual Unspecified Impurity	(b) (4)	
Total Impurities	(b) (4)	
Assay	(b) (4)	USP Monograph ^a Ph. Eur. Monograph ^b

^a Tested for drug substance from (b) (4) only.

^b Tested for drug substance from (b) (4) only.

^c (b) (4) acceptance criteria (b) (4) r than Ph. Eur. requirement.

(b) (4) HPLC=High performance liquid chromatography; Ph. Eur. =European Pharmacopoeia; USP=United States Pharmacopoeia

Calculated Daily Exposure for (b) (4) (ICH Q3C - (b) (4)

(b) (4)

The total daily exposure to (b) (4) calculated in the table above can be used to calculate the maximum amount of (b) (4) in two 900-mcg films as follows:

- Maximum Amount of (b) (4) (ppm) = Total Daily Exposure/Drug Product Weight of Two 900-mcg Films = (b) (4) ppm
- The maximum amount of (b) (4) ((b) (4) ppm) in drug product is (b) (4) than the ICH Q3C allowable limit of (b) (4) ppm. The calculated daily exposure for (b) (4) in the drug product meets the permitted daily exposure (PDE) requirement of (b) (4) mg/day and justifies the NMT (b) (4) ppm limit established for buprenorphine HCl manufactured by (b) (4)

Drug Product Degradants

The proposed acceptance criteria listed in the table below are consistent with test results observed during development as well as with the recommendations in ICH Q3B(R2), *Impurities in New Drug Products*, except for (b) (4). Note that (b) (4) and as such is considered qualified at the proposed acceptance criteria based on nonclinical testing.

In addition, for (b) (4) at the proposed buprenorphine active ingredient dosing range of 0.075 to 0.9 mg BID (0.15 to 1.8 mg/day), the qualification range of (b) (4) mg is (b) (4) % or (b) (4) mcg TDI (Total Daily Intake), whichever is lower according to ICH Q3B(R2). At (b) (4) % (b) (4) the TDI is (b) (4) mcg for the 1.8 mg buprenorphine daily dose, additional indication that the (b) (4) specification is supported.

Test	Acceptance Criteria	Method
Degradation Products (% w/w)		HPLC
(b) (4)	(b) (4)	
Unspecified Degradation Products		
Total Degradation Products		
Content Uniformity ^a	Meets USP <905> requirements (b) (4)	HPLC
Film Unit Weight ^a	Individual film weights within (b) (4)% of average film weight ^b	Gravimetric
Dissolution	Meets USP <711> requirements where Q= (b) (4)% at 60 minutes (b) (4)	HPLC, USP<711>
	(b) (4)	(b) (4)
pH ^a	(b) (4)	USP<791>
Microbiological Examination		USP<61>, USP<62>
<i>Staphylococcus aureus</i>	Negative	
<i>Pseudomonas aeruginosa</i>	Negative	
Total Combined Yeasts and Molds	(b) (4) CFU/unit	
Total Aerobic Microbial Count	(b) (4) CFU/unit	
Pouch Integrity ^a	(b) (4)	ASTM F1140

^a Release testing only.

^b (b) (4)

ASTM=American Society for Testing and Materials; AV=Acceptance value; CFU=Colony forming unit; HPLC=High performance liquid chromatography; USP=United States Pharmacopeia

Container/Closure System

Each individual buprenorphine hydrochloride buccal film (buprenorphine film) is packaged in a child-resistant, (b) (4)/foil (b) (4) package. The container closure was chosen to provide protection of the product from (b) (4) (reference DMF (b) (4) and DMF (b) (4) for detailed information). The compatibility between the product and the contact layer has been demonstrated through stability studies that were considered acceptable by the CMC reviewer? (refer to Product Quality review).

Extractables/Leachables

For this (b) (4) drug product, no extractables/leachables testing was conducted or is required based on safety assessment of active ingredient, all excipients, and analysis during stability studies when drug product was stored in container/closure system.

2.6 Proposed Clinical Population and Dosing Regimen

Belbuca is proposed for the management of pain severe enough to require daily, around-the-clock (ATC), long-term opioid treatment and for which alternative treatment options are inadequate in opioid-naïve and opioid-experienced patients.

Potentially chronic dosing is proposed at 75, 150, 300, 450, 600, 750, and 900 mcg BELBUCA up to twice daily.

2.7 Regulatory Background

BioErodable MuccoAdhesive (BEMA) buprenorphine (BELBUCA) has been developed as a two (2) component drug (BEMA and buprenorphine) starting with the preIND 72428 (submitted September 2, 2005) and the IND 72428 (original IND submitted December 15, 2005) with the intention of submitting a 505(b)(2) NDA. Transfer of this IND from BDSI to Endo Pharmaceuticals, Inc. (Endo) was made on January 6, 2012. Endo submitted a 505(b)(2) NDA for BELBUCA on December 23, 2014. Reference drugs are Buprenex (NDA 18401) and discontinued Subutex (NDA 20732). A generic drug product was examined for relative bioavailability (ANDA 79633, Roxane). Pivotal nonclinical testing of a BEMA is a 28-Day Buccal Toxicity Study of BEMA® buprenorphine in Beagle Dogs, submitted by BDSI as part of IND 72,428/NDA 205637 (BUNAVAIL™ (buprenorphine and naloxone) buccal film) which was approved June 6, 2014.

3 Studies Submitted

- **28-Day Buccal Toxicity Study of BEMA® Buprenorphine in Beagle Dogs ((b) (4) Study No.: 0436DB38.001)**
 - Originally submitted and reviewed with NDA 205637 for BUNAVAIL (buprenorphine and naloxone) buccal film

3.1 Studies Reviewed

- none.

3.2 Studies Not Reviewed

- none.

3.3 Previous Reviews Referenced

- IND 72428 (BEMA buprenorphine)
- IND 110267 (BEMA buprenorphine and naloxone)
- IND [REDACTED] (b) (4)
- NDA 205637 (BEMA buprenorphine and naloxone - BUNAVAIL)
- NDA 22266 (BEMA fentanyl – Onsolis)

4 Pharmacology

(Pharmacology is excerpted from Applicant's submission with some modification)

No new pharmacology studies were submitted with this NDA. The pharmacology of buprenorphine has been reported in the nonclinical literature and fully characterized to support other referenced, approved buprenorphine drug products, including NDA 18401 (Buprenex) and NDA 20732 (Subutex).

Safety pharmacology was evaluated as part of a 28-day repeat-dose toxicity study in dogs with buprenorphine buccal film three times daily submitted in support of NDA 205637 for BUNAVAIL and also submitted with this NDA. No cardiovascular safety or respiratory system effects were observed at the tested dose (750 mcg/dose, 2250 mcg/day buprenorphine). Anticipated opioid effects were observed on the central nervous system (abnormal gait, decreased activity, excessive salivation, and sporadic emesis) and gastrointestinal system (GI function - excessive salivation and sporadic emesis, transient body weight loss and food consumption decrease).

Proposed buccal sublingual buprenorphine exposure at the maximum recommended human dose (MRHD) of BEMA buprenorphine (1800 mcg/day) is less than that for the approved reference drug at the MRHD for Subutex (16 mg/day sublingual) and also for BEMA buprenorphine naloxone (BUNAVAIL 12.6 mg buccal).

5 Pharmacokinetics/ADME/Toxicokinetics

(This topic is excerpted from Applicant's submission with some modification)

The nonclinical pharmacokinetics/ADME/toxicokinetics of buprenorphine by various routes of administration has been characterized. The pharmacokinetic properties of buprenorphine in humans are presented in the prescribing information for Subutex sublingual tablets (NDA 20732) and the BUNAVAIL buccal film (NDA 205637).

Toxicokinetics information is used as it relates to the 28-day dog study with BEMA buprenorphine as originally submitted in support of NDA 205637 (BEMA buprenorphine and naloxone - BUNAVAIL) and submitted with this NDA. Proposed human MRHD blood levels are compared to nonclinical levels after exposure to BEMA buprenorphine in the Integrated Summary and Safety Evaluation (Section 11).

6 General Toxicology

6.1 Single-Dose Toxicity

- none.

6.2 Repeat-Dose Toxicity

The following study was originally submitted and reviewed in support of NDA 205637 for BUNAVAIL (buprenorphine and naloxone) buccal film, which was approved June 6, 2014. The study was submitted with this NDA and the template review is included here with minor modifications for completeness of this review.

Study title: 28-Day Buccal Toxicity Study of BEMA® Buprenorphine in Beagle Dogs

Study no.: (b) (4) Study No.: 0436DB38.001
Study report location: eCTD in DARRTS SDN 3
Conducting laboratory and location: (b) (4)
Date of study initiation: November 25, 2009
GLP compliance: yes
QA statement: yes
Drug, lot #, and % purity:
- BEMA discs with buprenorphine hydrochloride, Batch 7053049, NA
- BEMA disc without buprenorphine hydrochloride (BEMA placebo), Batch 7056839

Key Study Findings:

- Male and female beagle dogs were treated with BEMA placebo or BEMA buprenorphine (750 mcg disc) three times a day on the same buccal site for twenty eight consecutive days.
- Pharmacologically anticipated effects of buprenorphine were generally observed in the first week of treatment and included abnormal gait and stance, decreased activity, food particle emesis, excessive salivation, and transient weight loss (5-10%) and decreased food consumption.
- No other notable effects were observed. Only oral mucosa was evaluated histologically and both groups exhibited minimal to slight mixed cell infiltration of the oral mucosa.
- The BEMA buprenorphine dose of 750 mcg was a NOAEL with the largest toxicokinetic values of 92.59 ng•h/mL (AUC_{0-inf}) and 44.8 ng/mL (C_{max}) with no obvious local toxicity to the buccal mucosa.

Methods

Doses:

Group	Dose Level (mcg/dose)	Number of Animals	
		Male	Female
1. Control (BEMA Placebo)	0	3	3
2. BEMA Buprenorphine	750	3	3

Frequency of dosing: 3x/day at least 6 hours apart for 28 consecutive days

Route of administration: Buccal (same dose site for each administration)

Dose volume: NA

Formulation/Vehicle: BEMA disc (2.92 cm²) ± buprenorphine (0.808 mg/disc)

Species/Strain: Beagle dogs

Number/Sex/Group: 3/sex/dose

Age: 10-11 months at start of study

Weight: 7.5-10.9 kg at start of study

Satellite groups: none

Unique study design: - Dosing to same buccal site three time a day
- only 1 dose level

Deviation from study protocol: Nothing remarkable

Observations and Results

Mortality

Observation for mortality was performed twice daily on Days 1-28 and once prior to sacrifice on Day 29.

No mortality was observed.

Clinical Signs

Animals were observed prior to each dose administration and approximately one hour following each dose on Day 1 to Day 28 and additionally as necessary. A detailed observation of the application site was made prior to dosing on Days 1, 8, 15, 22 and 28. Animals were observed once prior to terminal sacrifice on Day 29.

Buprenorphine treatment-related signs included abnormal gait and stance, decreased activity, food particle emesis, and excessive salivation. These observations were noted mainly during the first week of treatment for the males but were observed throughout the 28-day treatment period for the females. These symptoms are expected pharmacological effects of buprenorphine.

Body Weights

Body weights were recorded for all animals at the time of randomization/selection and prior to the first dose administration on Days 1, 8, 15, 22 and 28. Body weights were

collected between 5 and 8 am. A fasted body weight was recorded prior to sacrifice on Day 29.

Body weight loss was observed for both the male (-5%) and female (-10%) buprenorphine treated groups during the first week of treatment, but not at statistically significant levels compared to the BEMA placebo group. Thereafter, males gained weight while females gained weight after the 2nd week (see tables).

Group Gender : Male	Study Phase : In-Life
Subject Gender : Male	

Period	Group ID:	M1	M2
Day 1 - 8	N	3	3
	Mean	-0.03	-0.57
	SD	0.115	0.351
Day 8 - 15	N	3	3
	Mean	0.00	0.17
	SD	0.100	0.153
Day 15 - 22	N	3	3
	Mean	0.00	0.40
	SD	0.100	0.100
Day 22 - 28	N	3	3
	Mean	0.03	0.17
	SD	0.289	0.231

Group Gender : Female	Study Phase : In-Life
Subject Gender : Female	

Period	Group ID:	F1	F2
Day 1 - 8	N	3	3
	Mean	0.07	-0.80
	SD	0.115	0.361
Day 8 - 15	N	3	3
	Mean	-0.07	-0.03
	SD	0.058	0.416
Day 15 - 22	N	3	3
	Mean	0.03	0.07
	SD	0.208	0.153
Day 22 - 28	N	3	3
	Mean	0.07	0.27
	SD	0.115	0.115

Food Consumption

Food consumption was recorded daily. Consumption was decreased during the first week of treatment but not to a statistically significant level as was observed for decreased body weights and was comparable to the BEMA Placebo group thereafter.

Ophthalmoscopy

Ophthalmology examinations were performed on all animals prior to treatment initiation and during the final week of treatment.

No buprenorphine treatment related effects were observed.

ECG

Electrocardiograms were obtained from all animals prior to treatment initiation and on Day 28. ECGs were obtained from all animals using right lateral recumbency. Recordings were made using limb leads I, II, III, aVR, aVL and aVF and two chest leads V1 and V2. Three leads were monitored simultaneously and a rhythm strip with two chest leads was obtained at the appropriate time intervals.

No buprenorphine treatment related effects were observed.

Hematology and Clinical Chemistry

Blood for evaluation of hematology, coagulation and clinical chemistry was collected from all animals prior to treatment initiation and prior to terminal sacrifice on Day 29. Blood for toxicokinetic evaluation was collected at selected time points on Days 1 and 28.

The following parameters were analyzed:

Hematology Parameters	
Red Blood Cell Count (RBC) and Morphology	Platelet count (PLT)
White Blood Cell Count (WBC)*	Hematocrit (HCT)
Mean Corpuscular Hemoglobin (MCH)	Hemoglobin (HGB)
Mean Corpuscular Hemoglobin Concentration (MCHC)	Reticulocyte Count (Retic)
Mean Corpuscular Volume (MCV)	
*Total and differential white blood cell counts, including neutrophils, basophils, eosinophils, monocytes, lymphocytes and large unstained cells	
Coagulation Parameters	
Activated Partial Thromboplastin Time (APTT)	Prothrombin Time (PT)

Clinical Chemistry Parameters	
Alanine Aminotransferase (ALT)	Globulin (calculated)(GLOB)
Albumin (ALB)	Glucose (GLU)
Albumin/Globulin ratio (calculated)(A/G)	Phosphorus (PHOS)
Alkaline Phosphatase (ALP)	Potassium (K)
Aspartate Aminotransferase (AST)	Sodium (NA)
Calcium (CA)	Total Bilirubin (T-BIL)
Chloride (CL)	Total Protein (TP)
Cholesterol (CHOL)	Triglycerides (TRIG)
Creatinine (CREAT)	Urea Nitrogen (BUN)

No buprenorphine treatment related effects were observed for hematology, coagulation, or clinical chemistry.

Urinalysis – none conducted

Gross Pathology

All animals were sacrificed on Day 29. Selected tissues were harvested at necropsy and selected organs were weighed.

A complete necropsy was performed on all animals that included examination of:

- The external body surface
- All orifices
- The cranial, thoracic, and abdominal cavities and their contents

All abnormalities were described completely and recorded. All animals necropsied had tissues collected and preserved as designated below in the histopathology section.

No gross abnormalities were observed in either group.

Organ Weights

The following organs were weighed:

Organs Weighed	
Adrenals	Testes
Brain	Ovaries
Heart	Spleen
Kidneys	Thyroids/parathyroids
Liver	

Organ to body weight ratios were calculated (using the final body weight obtained prior to necropsy), as well as organ to brain weight ratios.

No differences were observed between the two treatment groups organ weights.

Histopathology

For all animals necropsied, the tissues listed in the table below were preserved in 10% neutral buffered formalin (except for the testes that which were preserved in Bouin's fixative and eyes that were preserved in Davidson's).

Tissues Collected	
Cardiovascular	Urogenital
Aorta	Kidneys
Heart	Urinary Bladder
Digestive	Ovaries
Salivary gland(s)	Uterus
Tongue	Cervix
Esophagus	Vagina
Stomach	Testes
Small Intestine	Epididymides
Duodenum	Prostate
Jejunum	Endocrine
Ileum	Adrenals
Large Intestine	Pituitary
Cecum	Thyroid/Parathyroid
Colon	Skin/Musculoskeletal
Rectum	Skin
Pancreas	Mammary Gland
Liver	Skeletal Muscle (thigh)
Gallbladder	Femur with articular surface
Respiratory	Nervous/Special Sense
Trachea	Eye with optic nerve
Larynx	Sciatic Nerve
Lung with mainstem bronchus	Brain
Lymphoid/Hematopoietic	Spinal Cord – cervical
Sternum with bone marrow	Spinal Cord – midthoracic
Thymus	Spinal Cord – lumbar
Spleen	Lacrimal Glands
Lymph Nodes	Other
Mandibular	Animal Eartag
Mesenteric	Gross Findings
	Oral mucosa (treated and untreated)

The treated and untreated oral mucosa for all animals was evaluated microscopically.

Adequate Battery – yes, but only oral mucosa evaluated.

Peer Review – no.

Histological Findings – Nothing buprenorphine treatment related was observed. Both groups exhibited mixed cell infiltration of the oral mucosa (see tables on following page).

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0

			MALE
SEX :			
DOSE GROUP:	1	2	
NO.ANIMALS:	3	3	
<hr/>			
ORAL MUCOSA:TREATED :	3	3	
- Mixed cell infiltr. :	2	2	
Grade 1:	2	1	
Grade 2:	-	1	
<hr/>			
ORAL MUCOSA:UNTREAT :	3	3	
- Mixed cell infiltr. :	2	2	
Grade 1:	2	1	
Grade 2:	-	1	
<hr/>			
			FEMALE
SEX :			
DOSE GROUP:	1	2	
NO.ANIMALS:	3	3	
<hr/>			
ORAL MUCOSA:TREATED :	3	3	
- Mixed cell infiltr. :	2	2	
Grade 1:	2	1	
Grade 2:	-	1	
<hr/>			
ORAL MUCOSA:UNTREAT :	3	3	
- Mixed cell infiltr. :	2	3	
Grade 1:	2	2	
Grade 2:	-	1	
<hr/>			

Special Evaluation - none

Toxicokinetics

On Day 1, blood samples were collected immediately pre-dose and at 1, 2, 3, 4.5, and 6 hours after the first dose (immediate pre-dose 2). On Day 28, blood samples were collected immediately pre-dose and at 1, 2, 3, 4.5, 6 (immediate pre-dose 2), 9, and 24 hours after dose 1.

Toxicokinetic data showed good systemic exposure. Sex specific and combined TK data are presented below. Plasma levels of buprenorphine were higher in females compared to males on both Day 1 (mean AUC₀₋₆ 12% higher) and on Day 28 (mean AUC₀₋₆ 54% higher), possibly related to a fixed dose for both sexes with the mean body weight of the females at Day 28 (7.6 kg) was lower than that of the males (10.4 kg).

Plasma levels were lower at Day 28 when compared to Day 1 for both sexes suggesting possible increased metabolism.

Pharmacokinetic Parameters of Buprenorphine on Day 1 (Males and Females Combined)

Parameter	Treatment:			
	n	Mean	SD	CV%
T _{max} (hr)	6	1.17	0.41	34.99
T _{max} *		1.00 (1.00-2.00)		
C _{max} (ng/mL)	6	44.8	54.6	121.96
AUC ₀₋₆ (hr*ng/mL)	6	84.51	84.83	100.38
T _{last} (hr)	6	6.00	0.00	0.00
C _{last} (ng/mL)	6	6.58	8.00	121.68

Note: Full precision data used in pharmacokinetic analysis

*T_{max} presented in hours (hr) as Median [Range]

Pharmacokinetic Parameters of Buprenorphine for Males on Day 1

Parameter	Treatment:			
	n	Mean	SD	CV%
T _{max} (hr)	3	1.00	0.00	0.00
T _{max} *		1.00 (1.00-1.00)		
C _{max} (ng/mL)	3	37.3	19.7	52.70
AUC ₀₋₆ (hr*ng/mL)	3	79.87	38.86	48.66
T _{last} (hr)	3	6.00	0.00	0.00
C _{last} (ng/mL)	3	4.46	2.50	56.21

Note: Full precision data used in pharmacokinetic analysis

*T_{max} presented in hours (hr) as Median [Range]

Pharmacokinetic Parameters of Buprenorphine for Females on Day 1

Parameter	Treatment:			
	n	Mean	SD	CV%
T _{max} (hr)	3	1.33	0.58	43.30
T _{max} *		1.00 (1.00-2.00)		
C _{max} (ng/mL)	3	52.2	83.1	158.97
AUC ₀₋₆ (hr*ng/mL)	3	89.15	128.1	143.72
T _{last} (hr)	3	6.00	0.00	0.00
C _{last} (ng/mL)	3	8.70	11.8	136.21

Note: Full precision data used in pharmacokinetic analysis

*T_{max} presented in hours (hr) as Median [Range]

=====

Pharmacokinetic Parameters of Buprenorphine on Day 28 (Males and Females Combined)

Parameter	Treatment: BEMA Buprenorphine			
	n	Mean	SD	CV%
T _{max} (hr)	6	2.33	3.27	139.97
T _{max} *			1.00 (1.00-9.00)	
C _{max} (ng/mL)	6	28.8	21.3	73.90
AUC ₀₋₆ (hr*ng/mL)	6	47.27	29.57	62.55
AUC ₀₋₂₄ (hr*ng/mL)	6	81.34	30.75	37.81
AUC _{inf} (hr*ng/mL)	5	92.59	26.85	29.00
AUC _{Extrap} (%)	5	3.60	1.82	50.61
λ _z (1/hr)	5	0.1232	0.0297	24.11
T _{1/2} (hr)	5	5.89	1.39	23.61
T _{last} (hr)	6	24.00	0.00	0.00
C _{last} (ng/mL)	6	0.431	0.219	50.85

Note: Full precision data used in pharmacokinetic analysis

*T_{max} presented in hours (hr) as Median [Range]

Pharmacokinetic Parameters of Buprenorphine for Males on Day 28

Parameter	Treatment: BEMA Buprenorphine			
	n	Mean	SD	CV%
T _{max} (hr)	3	3.67	4.62	125.97
T _{max} *			1.00 (1.00-9.00)	
C _{max} (ng/mL)	3	27.1	30.9	113.80
AUC ₀₋₆ (hr*ng/mL)	3	37.23	41.94	112.65
AUC ₀₋₂₄ (hr*ng/mL)	3	65.02	36.54	56.20
AUC _{inf} (hr*ng/mL)	2	79.46	42.81	53.88
AUC _{Extrap} (%)	2	3.50	1.54	44.05
λ _z (1/hr)	2	0.1110	0.0153	13.76
T _{1/2} (hr)	2	6.30	0.87	13.76
T _{last} (hr)	3	24.00	0.00	0.00
C _{last} (ng/mL)	3	0.440	0.295	66.98

Note: Full precision data used in pharmacokinetic analysis

*T_{max} presented in hours (hr) as Median [Range]

Pharmacokinetic Parameters of Buprenorphine for Females on Day 28

Parameter	Treatment: BEMA Buprenorphine			
	n	Mean	SD	CV%
T _{max} (hr)	3	1.00	0.00	0.00
T _{max} *			1.00 (1.00-1.00)	
C _{max} (ng/mL)	3	30.5	13.2	43.10
AUC ₀₋₆ (hr*ng/mL)	3	57.31	11.15	19.45
AUC ₀₋₂₄ (hr*ng/mL)	3	97.65	15.19	15.56
AUC _{inf} (hr*ng/mL)	3	101.4	15.43	15.22
AUC _{Extrap} (%)	3	3.66	2.33	63.59
λ _z (1/hr)	3	0.1313	0.0374	28.50
T _{1/2} (hr)	3	5.61	1.79	31.89
T _{last} (hr)	3	24.00	0.00	0.00
C _{last} (ng/mL)	3	0.421	0.181	42.92

Note: Full precision data used in pharmacokinetic analysis

*T_{max} presented in hours (hr) as Median [Range]

Dosing Solution Analysis

Three months stability indicated for BEMA placebo and BEMA buprenorphine for this 28-day study. The batch of BEMA buprenorphine used in this test conformed with scale up, registration, and post-registration batch analyses.

7 Genetic Toxicology

N/A - 505(b)(2) to NDA 20732 (Subutex)

8 Carcinogenicity

N/A - 505(b)(2) to NDA 20732 (Subutex)

9 Reproductive and Developmental Toxicology

N/A - 505(b)(2) to NDA 20732 (Subutex)

10 Special Toxicology Studies

- none.

11 Integrated Summary and Safety Evaluation

Introduction

This 505(b)(2) submission relies on safety information from Subutex (NDA 20732 – buprenorphine sublingual tablet) and comparative bioavailability of Subutex and BEMA buprenorphine (Belbuca). In addition, a 28-day dog study with BEMA buprenorphine was submitted as part of NDA 205637 (BUNAVAIL – BEMA buprenorphine and naloxone) to support clinical safety in regard to potential local toxicity with repeated applications of the BEMA disc with buprenorphine. Systemic exposure to buprenorphine was also assessed in the nonclinical study. Of note is that, based on preIND advice for BUNAVAIL, we informed the Sponsor that no chronic local toxicity study would be necessary if the to-be-marketed product established acceptable bioequivalence to Subutex and local toxicity was adequately evaluated in clinical studies. This caveat from the preIND was demonstrated and also is relevant for this NDA regarding buprenorphine exposure and local toxicity.

Bioavailability and Comparability of Dose Levels

Comparable bioavailability of buprenorphine for Subutex and Belbuca has been demonstrated in clinical studies. The maximum recommended human dose (MRHD) or

target dose of Subutex for opioid dependence is 16 mg buprenorphine as listed in the Subutex label. This Subutex dose is substantially larger than the proposed buprenorphine dose at the MRHD for Belbuca of 1.8 mg/day (900 mcg BID) for pain. Therefore, the Subutex human data supports the proposed Belbuca pain dosing thereby allowing use of other nonclinical data related to buprenorphine from Subutex to be used in support of the Belbuca 505(b)(2) submission in the product label (e.g., reproductive toxicity, carcinogenicity, mutagenicity). In addition, the long-term use of approved buprenorphine sublingual tablets in Subutex sufficiently supports the proposed dosing and long-term use of Belbuca.

Drug Formulation

Review of the composition of the drug substances and drug product did not identify any nonclinical-based safety issues related to impurities, degradants, and excipients (see section 2.3 Drug Formulation). Proposed chronic dosing with Belbuca containing these inactive ingredients was supported by being listed in the FDA Inactive Ingredient Database, being declared by FDA as generally recognized as safe (GRAS), and/or by available toxicology information on the inactive ingredients in the literature. See review of NDA 205637 (BEMA buprenorphine and naloxone – BUNAVAIL).

Nonclinical Data and Safety Margins

The only nonclinical study submitted was a 28-day buccal dog study with the proposed drug product, BEMA buprenorphine (Belbuca), in which the BEMA film was administered to the same buccal site three times a day for 28 consecutive days. Other than known pharmacological effects of buprenorphine (e.g., abnormal gait and stance, decreased activity, food particle emesis, and excessive salivation, transient weight loss (5-10%) and decreased food consumption), no other buprenorphine-related effects were observed compared to BEMA placebo. The only local toxicity for both groups included minimal to slight inflammatory cell infiltration of the oral mucosa. The BEMA buprenorphine film used in the 28-day dog study was 2.92 cm² and contained 808 mcg buprenorphine/disc (~276 mcg/cm²). The largest Belbuca proposed dose for approval is 2.801 cm² and contains ~900 mcg buprenorphine (321 mcg/cm²) or ~1.2-fold more buprenorphine per cm² than in the nonclinically tested test article. These differences are considered of minimal importance for assessing local toxicity at a 20% difference in concentration with repeated dosing. There is no issue regarding potential systemic toxicity as blood levels will be used to compare animal and human exposure. Therefore, all drug product components were tested at the clinically relevant concentrations.

While the dogs were dosed three times a day and humans will be dosed up to twice a day, based on these slight concentration differences, the local toxicity of buprenorphine in BEMA buprenorphine cannot be absolutely used to identify and assess potential local toxicity from Belbuca, but is considered an adequate assessment. What can be noted for the dog dosing is that three repeated daily doses to the same buccal dose site did not result in any overt local toxicity. On this basis, the data from the 28-day dog study

can be used to assess potential local toxicity and compare systemic exposure of buprenorphine from BEMA buprenorphine to that for Subutex and Belbuca. To this end, the buprenorphine C_{max} and AUC values in the dogs at a No Observed Adverse Effect Level (NOAEL - ~2.25 mg/kg/day) were comparable to or greater than buprenorphine values for Subutex at the maximum recommended human dose (MRHD) of 16 mg buprenorphine. Although not needed to support the proposed human dosing because acceptable Subutex and Belbuca bioavailability has been demonstrated, nonclinical support for the proposed human systemic exposure to buprenorphine from use of Belbuca exists. Human dosing is also supported for potential local toxicity of the BEMA film alone. Animal NOAELs compared to the highest proposed human dose ratios (safety margins – SM) are considered adequate when the animal:human ratio is ≥1, which is the case for the highest proposed human dose of 900 mcg BID (1.8 mg/day) as listed in the table. Interestingly, the dog data also supports the safety of the approved maximum Subutex dose regarding systemic toxicity (see table).

Subutex (tablet) and Belbuca (BEMA Buprenorphine) Pharmacokinetic Values for Buprenorphine in Humans at Maximum Recommended Dose Compared to Those from 28-Day Dog Study with BEMA Buprenorphine (BB)						
Species	Drug	Buprenorphine Dose (mg)	C _{max} (ng/mL)	AUC _{0-∞} (ng*h/mL)	Safety Margin (dog ÷ human)	
					C _{max}	AUC
Human	Subutex	16 ^a	9.4	94.18	3.1	0.98
	Belbuca	0.9 BID ^b	2.64	19.1	10.9	4.8
Dog ^c	Belbuca	0.75 TID ^c	28.8	92.59	--	--

a – from Subutex label study report 20-A79-AU

b - extrapolated from single 900 mcg dose (x2 for proposed BID dosing) – study report BUP-118

c - at NOAEL for local toxicity (BEMA and BEMA buprenorphine) and systemic toxicity (buprenorphine)

Summary

Based on nonclinical review of the information as listed above, NDA 207932 (Belbuca) may be approved with no other comments.

12 Appendix/Attachments

- none.

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/s/

GARY P BOND
09/17/2015

JAY H CHANG
09/17/2015

RICHARD D MELLON
09/17/2015

I concur with Dr. Bond's recommendation that NDA 207932 may be approved from the nonclinical pharmacology toxicology perspective.