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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 205637
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Sponsor's letter date: July 31, 2013
CDER stamp date: August 7, 2013
Product: BUNAVAIL™
(BEMA Buprenorphine NX, BNX, BioErodible
MucoAdhesive Buprenorphine Naloxone)
Indication: Opioid dependence
Sponsor: BioDelivery Sciences International, Inc. (BDSI)
Review Division: Division of Anesthesia, Analgesia, and Addiction
Products
Reviewer: Gary P. Bond. Ph.D.
Supervisor/Team Leader: Adam M. Wasserman, Ph.D.
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Project Manager: Matthew W. Sullivan, M.S.

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1 Executive Summary

1.1 Introduction (Background and Regulatory Issues)

BEMA Buprenorphine NX (BNX; BUNAVAIL™) is an oral transmucosal form of buprenorphine hydrochloride and naloxone hydrochloride dihydrate intended for application to the buccal mucosa. This drug product consists of buprenorphine and naloxone in separate, attached BioErodible MucoAdhesive (BEMA) discs. This design is to enable buccal absorption of buprenorphine with minimal systemic absorption of naloxone while achieving co-extraction of naloxone with buprenorphine as a tamper-resistant formulation to reduce abusability under conditions of attempted drug abuse.

The intended indication is opioid dependence. Buprenorphine is a synthetic opioid that is classified as a μ -opioid receptor partial agonist and a Schedule III controlled substance in the United States (US). Nonclinical and clinical research indicates that buprenorphine has an extended duration of action due to the receptor binding and central nervous system diffusion characteristics of the molecule. Naloxone is a competitive antagonist of μ -, δ -, and κ -opioid receptors with no opioid agonist activity, and is included in the drug product as an abuse deterrent.

This 505(b)(2) submission relies the Agency's prior finding of safety and efficacy of Suboxone (NDA 20-733 – buprenorphine and naloxone sublingual tablet) as reflected in the approved label and is supported by a comparative bioavailability evaluation of the two drugs. In addition, a 28-day dog study with BEMA buprenorphine (no naloxone), which was not needed to support human safety based on the comparative human bioavailability of Suboxone and BNX, was submitted regarding potential local toxicity with repeated applications of the BEMA disc with only buprenorphine (no naloxone) which also described systemic buprenorphine exposure.

The following comments were provided to the sponsor as preIND minutes for IND 110,267 related to the original IND submission and the drug development program (meeting of January 18, 2011):

Provided clinical exposures to BEMA Buprenorphine NX are within that of the listed drug, Suboxone, and with adequate monitoring for local toxicity in clinical trials, nonclinical studies to support the drug product during clinical development will not be necessary except as needed to address impurities which exceed ICH guidelines or the presence of novel excipients by identity, route, level, or duration. In the absence of sufficient safety support of novel excipients from prior inclusion in approved products, information from literature or other sources, a chronic 9-month buccal study will need to be conducted using a placebo BEMA patch.

As will be described, based on the information contained in the NDA submission, as comparable bioavailability was demonstrated between Suboxone and BNX, no nonclinical studies were necessary.

1.2 Brief Discussion of Nonclinical Findings

The only nonclinical study submitted was a 28-day buccal dog study with BEMA buprenorphine (IND (b)(4)) in which the BEMA buprenorphine disc was administered to the same buccal site three times a day for 28 consecutive days. Note that this was not the proposed drug product BNX as there was no naloxone in the nonclinically tested material. Other than known pharmacological effects of buprenorphine, no other buprenorphine-related effects were observed compared to BEMA placebo. The only local toxicity noted for both groups included minimal to slight cell infiltration of the oral mucosa. The BEMA buprenorphine disc used in the 28-day dog study was 2.92 cm² and contained 0.808 mg buprenorphine/disc (~0.257 mg/cm²) and the BNX disc to be marketed contains ~964 mg/cm² or ~3.8-fold more buprenorphine per cm² than in the nonclinical test article. While the dogs were dosed three times a day, based on these concentration differences, the local toxicity of buprenorphine in BEMA buprenorphine cannot be used to identify and assess potential local toxicity from BNX but it can for the potential local toxicity of excipients in the BEMA disc. 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. Regardless, the data from the 28-day dog study can really only be used to compare systemic exposure of buprenorphine from BEMA buprenorphine to that for Suboxone and BNX. To this end, the buprenorphine C_{max} and AUC values in the dogs at a No Observed Adverse Effect Level (NOAEL) were comparable to or greater than buprenorphine values for Suboxone at the maximum recommended daily maintenance dose (MRDMD) of 24 mg buprenorphine and its bioequivalent dose of BNX of 12.6 mg buprenorphine, indicating nonclinical support for the proposed human systemic dosing for buprenorphine. While the safety of application of the BEMA disc itself is supported based on negligible local toxicity in the 28-day study, as this is not the “to be marketed” product formulation, human dosing cannot be supported by the nonclinical data.

This 505(b)(2) application is based on the Agency’s prior finding of Safety and Efficacy of NDA 20-733 (Suboxone – sublingual tablets). The recommended daily maintenance dose (RDMD) or target dose of Suboxone for opioid dependence is 16/4 mg buprenorphine/naloxone as listed in the Suboxone label. However, the daily maintenance dose is generally in the range of 4/1 mg to 24/6 mg buprenorphine/naloxone per day depending on the individual patient. The 24/6 Suboxone dose is equivalent to a BNX dose of 12.6/2.09 mg buprenorphine/naloxone based on buprenorphine exposure. Dosages higher than this have not been demonstrated to provide any clinical advantage as listed in the current Suboxone label. Therefore, the Suboxone human data supports the proposed BNX dosing allowing use of nonclinical data related to buprenorphine and naloxone from the approved Suboxone label to be used in support of the BNX 505(b)(2) submission (e.g., reproductive toxicity, carcinogenicity, mutagenicity). In addition, the long-term use of approved, combined buprenorphine and naloxone sublingual tablets in Suboxone sufficiently supports the proposed combined dosing and long-term use of BNX.

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

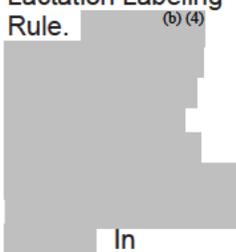
1.3 Recommendations

1.3.1 Approvability

NDA approval is recommended from the nonclinical perspective. The results of relative bioavailability clinical trials using approved Suboxone and proposed BNX indicate that systemic exposure to buprenorphine is comparable and does not exceed approved systemic exposure levels for Suboxone at the maximum recommended daily maintenance dose for BNX. The buprenorphine systemic exposure comparability provides support for systemic safety. In addition, nonclinical data provide evidence for human safety for the expected systemic exposure to buprenorphine and potential local toxicity from BEMA buprenorphine discs. Potential local toxicity to BNX is also considered to be adequately addressed by long term use of Suboxone and the lack of any overt local toxicity from BNX in clinical studies and trials conducted as part of this NDA.

1.3.2 Additional Nonclinical Recommendations – none.

1.3.3 Labeling

Pharm/Tox-related Labeling Sections for NDA 205637		
Label Proposed by Applicant - from current Suboxone sublingual tablets label (10-23-13)	FDA-Proposed label - adjusted for the proposed PLLR (Pregnancy and Lactation Labeling Rule) as of the date of this review	Rationale for Difference
<p style="text-align: center;">Highlights -----Use in Specific Populations-----</p> <ul style="list-style-type: none"> •  (b) (4) •  (b) (4) 	<p style="text-align: center;">Highlights -----Use in Specific Populations-----</p> <ul style="list-style-type: none"> • Pregnancy: Based on animal data, may cause fetal harm. (8.1) • Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3) 	<p>FDA-proposed information based on Zubsolv label (July 2013)</p>
<p>8. USE IN SPECIFIC POPULATIONS</p> <p>8.1. Pregnancy</p> <p>Pregnancy Category C.</p> <p>There are no adequate and well-controlled studies of BUNAVAIL™ buccal film or buprenorphine/naloxone in pregnant women. BUNAVAIL™ buccal films should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</p>	<p>8. USE IN SPECIFIC POPULATIONS</p> <p>8.1. Pregnancy</p> <p>Pregnancy Category C.</p> <p><i>Risk Summary</i></p> <p>There are no adequate and well-controlled studies of Bunavail or buprenorphine/naloxone in pregnant women. Limited published data on use of buprenorphine, the active ingredient in Bunavail, 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 post-natal development studies in rats demonstrated dystocia, increased neonatal deaths, and developmental delays. 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. Embryofetal death was also observed in both rats and</p>	<p>Use PLLR and MHC "hybrid" label. Applicant's text matches approved Suboxone sublingual tablets label (NDA 20733), the referenced approved NDA.</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.  (b) (4)</p> <p> In collaboration with the Maternal Health Team (MHT), an overall Risk Summary has also been added.</p>

	<p>rabbits. (See <i>Animal Data</i>)</p> <p>Bunavail buccal film should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</p> <p><i>Clinical Considerations</i></p> <p><i>Disease-associated maternal and embryo-fetal risk</i></p> <p>Opioid dependence in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death.</p> <p><i>Fetal/neonatal adverse reactions</i></p> <p>Neonatal abstinence syndrome may occur in newborn infants of mothers who were on buprenorphine maintenance treatment. Observe newborns for poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly. [See <i>Warnings and Precautions (5.9)</i>]</p> <p><i>Labor or Delivery</i></p> <p>As with all opioids, use of buprenorphine prior to delivery may result in respiratory depression in the newborn. Closely monitor neonates for signs of respiratory depression. An opioid antagonist such as naloxone should be available for reversal of opioid induced respiratory depression in the neonate.</p> <p><i>Data</i></p> <p><i>Human Data</i></p> <p>Studies have been conducted to evaluate neonatal outcomes in women exposed to buprenorphine during pregnancy. Limited published data on malformations from trials, observational studies, case series, and case reports on buprenorphine use in pregnancy have not shown an increased risk of major malformations. Based on these studies the incidence of neonatal abstinence syndrome is not clear and there does not appear</p>	<p>A statement regarding the comparability of exposure margins for Suboxone and Bunavail has been added. See discussion below this table for details.</p> <p>Text from Clinical considerations to Human Data from Zubsolv label.</p>
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<p>(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 (b) (4) buccal 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 buprenorphine exposure approximately 20 times and 35 times, respectively, the recommended human (b) (4) buccal dose (b) (4)). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in (b) (4). 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 number of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated buprenorphine exposure approximately 6 times the recommended human (b) (4) buccal dose (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 rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in</p>	<p>to be a dose-response relationship.</p> <p><i>Animal Data</i></p> <p>Bunavail 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 dose of 16 mg buprenorphine via Suboxone, which is equivalent to a human buccal dose of 8.4 mg buprenorphine via Bunavail.</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 buccal dose (RHD)). 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 RHD). 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 RHD). 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</p>	
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<p>resorptions, occurred at 30 mg/kg/day.</p> <p>Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated (b) (4) exposure was approximately 3 and 6 times, respectively, the recommended human (b) (4) buccal dose (b) (4)), after IV doses up to 0.8 mg/kg/day (estimated (b) (4) exposure was approximately 0.5 times and equal to, respectively, the recommended human (b) (4) buccal dose (b) (4)), or after oral doses up to 160 mg/kg/day in rats (estimated (b) (4) exposure was approximately 95 times the recommended human (b) (4) buccal dose (b) (4)) and 25 mg/kg/day in rabbits (estimated (b) (4) exposure was approximately 30 times the recommended human (b) (4) buccal dose (b) (4)). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated (b) (4) exposure was approximately 0.6 times the recommended human (b) (4) buccal 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 (b) (4) exposure was approximately 6 times the recommended human (b) (4) buccal dose of (b) (4)) or oral administration of 1 mg/kg/day or greater (estimated (b) (4) exposure was approximately equal to the recommended human (b) (4) buccal 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</p>	<p>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 RHD), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the RHD), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the RHD) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the RHD). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the RHD), 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 RHD) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the RHD) were not statistically significant. 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 RHD).</p> <p>Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the RHD). 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 RHD),</p>	
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<p>0.2 mg/kg/day or greater (estimated (b) (4) exposure approximately 0.3 times the recommended human (b) (4) buccal dose (b) (4)).</p> <p>(b) (4)</p> <p>Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily (b) (4) dose of (b) (4) mg on a mg/m² basis). Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases (b) (4) in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human (b) (4) buccal dose (b) (4)), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human (b) (4) buccal dose (b) (4)), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human (b) (4) buccal dose (b) (4)).</p> <p>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) buccal dose (b) (4)).</p>	<p>after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the RHD), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the RHD). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. 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 RHD).</p>	
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<p>13. NONCLINICAL TOXICOLOGY</p> <p>13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility</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 buprenorphine exposure was approximately 4, 18, and 44 times the recommended human buccal dose (b)(4) 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 (b)(4) buccal dose (b)(4)) 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 CD-1 mice, buprenorphine was not carcinogenic</p>	<p>13. NONCLINICAL TOXICOLOGY</p> <p>13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>Bunavail 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 buccal dose of 8.4 mg buprenorphine via Bunavail.</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 buccal dose of 8.4 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 RHD) 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 CD-1 mice, buprenorphine was not</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 Zubsolv has been added. See discussion below this table for details.</p>
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<p>at dietary doses up to 100 mg/kg/day (estimated buprenorphine exposure was approximately 30 times the recommended human ^{(b) (4)} buccal dose ^{(b) (4)}).</p> <p>Mutagenicity:</p> <p>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 in vitro cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat.</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. 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 [³H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.</p> <p>Impairment of Fertility:</p> <p>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 ^{(b) (4)} buccal dose ^{(b) (4)}) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100</p>	<p>carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the RHD).</p> <p>Mutagenicity:</p> <p>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.</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 (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 [³H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.</p> <p>Impairment of Fertility:</p> <p>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 RHD), produced a reduction in fertility demonstrated by reduced female</p>	
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<p>ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human ^{(b) (4)} buccal dose ^{(b) (4)}) had no adverse effect on fertility.</p>	<p>conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the RHD) had no adverse effect on fertility.</p>	
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2 Drug Information

2.1 Drug

Buprenorphine Hydrochloride

CAS Registry Number – 53152-21-9

Generic Name - buprenorphine

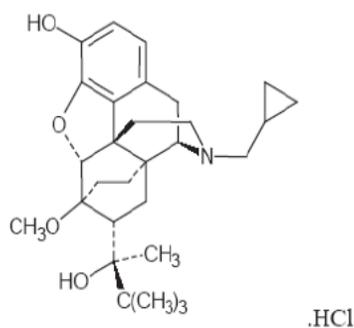
Code Name – none reported

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

Structure or Biochemical Description



Pharmacologic Class – a μ -opioid receptor partial agonist

Naloxone Hydrochloride Dihydrate

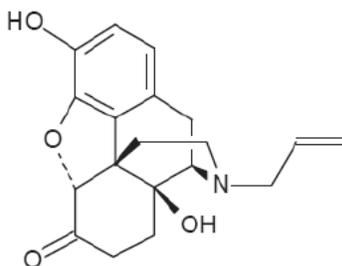
CAS Registry Number - 51481-60-8

Generic Name - naloxone

Code Name - 1492

Chemical Name - morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5 α)-, dihydrateMolecular Formula/Molecular Weight
C₁₉H₂₁NO₄•HCl•2H₂O/399.87

Structure or Biochemical Description

HCl • 2H₂O

Pharmacologic Class - opioid antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 110,267 (BEMA Buprenorphine NX)

(b) (4)

NDA 22-266 (BEMA fentanyl; Onsolis)

NDA 20-733 (Suboxone – buprenorphine and naloxone sublingual tablets)

NDA 20-732 (Subutex – buprenorphine sublingual tablets)

NDA 22-410 (Suboxone sublingual film)

DMF (b) (4) – Buprenorphine hydrochloride

DMG (b) (4) – Naloxone hydrochloride

2.3 Drug Formulation

Drug Substance

Buprenorphine hydrochloride - The specifications for buprenorphine hydrochloride by the drug substance manufacturer, (b) (4), are listed in the table below. The

(b) (4) specification complies with the USP monograph, with additional testing for related substances to comply with the European Pharmacopeia (EP) monograph, for chloride assay to comply with a request from the FDA, for residual solvents, and for particle size analysis. Testing for heavy metals is not performed routinely because analysis of three batches by inductively coupled plasma emission spectrophotometry has determined that the levels were (b) (4). For additional details, please refer to Drug Master File (DMF) (b) (4).

At a maximum recommended daily maintenance dose (MRDMD) dose of 12.6 mg buprenorphine/day, ICH 3A guidance has a qualification specification of NMT 0.15% or 1.0 mg per day intake (whichever is lower) (b) (4). The level of the residual solvent (b) (4) specification ((b) (4)) is also allowed according to ICH Q3C (Tables and List) as this higher than the listed allowed level of (b) (4) ppm is acceptable based on manufacturing capability and good manufacturing practice (GMP). ONDQA agrees with this assessment plus notes that (b) (4) is not used in the manufacturing process of the drug product.

(b) (4) Specification for Buprenorphine Hydrochloride

Test	(b) (4) Acceptance Criteria ¹
Appearance	White or off-white crystalline powder, free from visible evidence of contamination
Identity: A) IR (USP<197K>) B) Titration C) Chloride (USP<191>)	Complies with USP tests A, B and C
(b) (4)	(b) (4) %
Residue on ignition (USP<281>)	NMT (b) (4) %
pH (USP<791>)	4.0 to 6.0
Related substances (EP): ² PhEur Impurity (b) (4) PhEur Impurity Individual impurities Total impurities	NMT (b) (4) % NMT % NMT % NMT %
Chromatographic purity (USP): Individual impurity Total impurities	NMT (b) (4) % NMT %
Specific optical rotation (USP<781S>)	-92° to -98°
Water (USP<921> method I)	NMT (b) (4) %
Assay	98.5% to 101.0%
Residual solvents: (b) (4)	NMT (b) (4)
Particle Size	D10 NMT (b) (4) μm D50 NMT μm D90 NMT μm

(b) (4)

Naloxone Hydrochloride Dihydrate – The specifications for buprenorphine hydrochloride by the drug substance manufacturer, (b) (4), are listed in the table below. The specification complies with the USP monograph, with additional testing for related substances to comply with the European Pharmacopeia (EP) monograph. For additional details, please refer to Drug Master File (DMF) (b) (4).

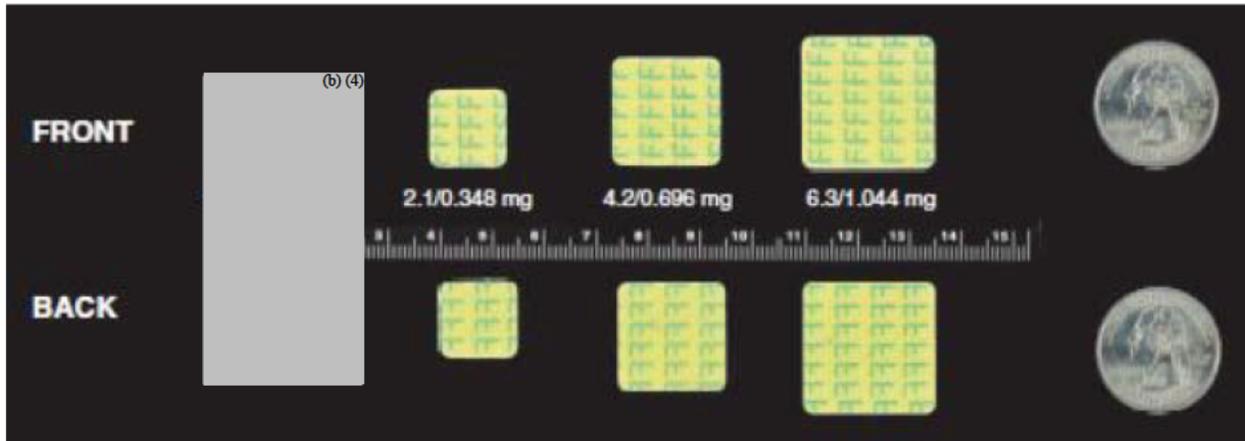
At the MRDMD for naloxone of 2 mg, the qualification threshold is 0.15% or 1.0 mg per day intake (whichever is lower) per ICH Q3A guidance. On this basis no qualification is required for the related substances at 0.15% max levels. For (b) (4), a structural alert, the potential dose is (b) (4) mcg at (b) (4) % which is acceptable according to CDER Guidance for Industry - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (Dec. 2008). On this basis, European Pharmacopiea (EP) Impurity (b) (4) can be ignored at a (b) (4) % level). For the other proposed EP impurities levels at (b) (4) % max are within the drug substance specifications of the referenced product and have been deemed acceptable by the Agency.

(b) (4) Specification for Naloxone Hydrochloride Dihydrate

Test	(b) (4) Acceptance Criteria ¹
Appearance	White or almost white powder
Identivty by IR, USP<197K>	Matches standard
(b) (4)	(b) (4) %
Loss on Drying (hydrous form), USP<731>	11.0% max
Specific Rotation, USP<781S>	-170° to -181°
Assay (dried basis), titration, USP	98.0% to 100.5%
Related substances (TLC, USP): (b) (4) and other impurities	(b) (4) % max
Related Substances (HPLC, CAR#940907): (b) (4)	(b) (4) % w/w (b) (4) % w/w max % w/w max % w/w max % w/w max % w/w max % w/w max % w/w max
Unknown (each) Total	% w/w max % w/w max
Related Substances (MS-HPLC, VR#777): (b) (4)	(b) (4) % w/w
Identification, UV A ₂₈₁ /A ₂₆₂	1.55 to 1.95
Sieve Test US Std. No. 40	100% through
Melting Range, USP<741>	177 to 180°C
Identification B (TLC), EP<2.2.27>	Matches standard
Identification C (Chloride), EP<2.3.1>	White precipitate
Appearance of Solution, (EP 2.2.1 and 2.2.2, Method II): Degree of Clarity Degree of Coloration	Clear Colorless
Acidity or Alkalinity (EP)	0.2 mL max
Specific Optical Rotation, (20°C), EP<2.2.7>	-170 to -181°
Related Substances (EP<2.2.29>): EP Impurity (b) (4) EP Impurity EP Impurity EP Impurity EP Impurity EP Impurity Unknown related substances Total related substances	(b) (4) max max max max max max max max max (b) (4) %
Water (EP<2.5.12>) (b) (4) EP<2.4.14>	(b) (4) % max
Assay (Titration, EP)	98.0 to 102.0% (b) (4)

Drug Product

The drug product appearance with buprenorphine/naloxone dose (964 mcg/cm² buprenorphine/160 mcg/cm² naloxone), dimensions, and composition (entire disc – mucoadhesive and backing layers combined) are as follows (note that the lowest proposed dosage will not be approved based on CMC and/or ClinPharm issues - see those reviews for more details):



Approximate Dimensions of BEMA[®] Buprenorphine NX Films

Strength (mg)	Area (cm ²)	Length (mm)	Width (mm)
2.1/0.348	2.179	14.876	14.876
4.2/0.696	4.357	20.956	20.956
6.3/1.044	6.536	25.632	25.632

BEMA[®] Buprenorphine NX Film Composition

Component	% w/w	Strength (mg Buprenorphine/naloxone free base)			
		(b) (4)	2.1/0.348	4.2/0.696	6.3/1.044
Purified Water ¹	-	-	-	-	
Buprenorphine Hydrochloride	3.456	(b) (4)	2.264	4.527	6.791
Propylene Glycol		(b) (4)			
Sodium Benzoate		(b) (4)			
Methylparaben		(b) (4)			
Propylparaben		(b) (4)			
Ferric Oxide, Yellow		(b) (4)			
Citric Acid, (b) (4)		(b) (4)			
Vitamin E Acetate		(b) (4)			
Monobasic Sodium Phosphate, (b) (4)		(b) (4)			
Polycarbophil		(b) (4)			
Hydroxypropyl Cellulose		(b) (4)			
Hydroxyethyl Cellulose		(b) (4)			
Carboxymethylcellulose Sodium		(b) (4)			
Sodium Hydroxide		(b) (4)			
Dibasic Sodium Phosphate, (b) (4)		(b) (4)			
Saccharin Sodium		(b) (4)			
Citrus Blend Flavor		(b) (4)			
Naloxone Hydrochloride	0.650	(b) (4)	0.425	0.850	1.275
(b) (4) Blue Ink		(b) (4)			(b) (4)
Total Weight (mg)	100.00	(b) (4)	65.492	130.985	196.477
					(b) (4)

Drug Product Specifications

1. The recommended daily maintenance dose (RDMD) for Suboxone is a target dose of 16/4 mg Buprenorphine/Naloxone. It is this value of 16 mg daily dose of buprenorphine in Suboxone that is used for nonclinical labeling section purposes. The maintenance dose of Suboxone sublingual tablet is generally in the range of 4/1 mg buprenorphine/naloxone to 24/6 mg buprenorphine/naloxone per day depending on the individual patient. Dosages higher than this have not been demonstrated to provide any clinical advantage as listed in the current Suboxone label.

Based on the pharmacokinetic bioavailability data of buprenorphine from clinical study BNX-101, the RDMD for BNX would be 8.4/1.4 mg for BNX as equivalent to 16/4 mg Suboxone. For the maintenance dose range of Suboxone (4/1 to 24/6 mg), the equivalent values to achieve similar buprenorphine levels for BNX would be (b) (4) to 12.6/2.09 mg (12.6/2.09 being the MRDMD).

According to the ICH Q3B Guidance for drug products, for total doses of buprenorphine and naloxone <10 mg as the identified daily maintenance dose,

the qualification threshold for impurities/degradants is 1.0% or 50 µg Total Daily Intake (TDI), whichever is lower. Total doses of 10-100 mg have qualification thresholds of 0.5% or 200 µg TDI, whichever is lower. The proposed impurity/degradant specifications are as follows:

Proposed Drug Product Specifications for BEMA[®] Buprenorphine NX



For buprenorphine, the RDMD at 8.4 mg, based on bioequivalence to 16 mg Suboxone, yields a dose of 84 µg/day at 1% so the impurity/degradant specification should be NMT 0.6% for buprenorphine-related impurities/degradants to satisfy the 50 µg per day maximum intake allowed (8.4 mg x 0.6% = 50 µg). An upper dose range dose of 12.6 mg yields a dose of 63 µg/day at 0.5% so the impurity/degradant specification is acceptable as the buprenorphine-related impurities/degradants satisfy the 200 µg TDI allowed (12.6 mg x 0.63% = 50 µg). As listed above in the specifications table, except for the lowest dosage form of (b) (4) mg BNX all other dosage forms specifications are set at (b) (4)%.

The maintenance dose of naloxone at the upper dose range of 2.09 mg yields an impurity/degradant dose of 21 µg/day at 1% for naloxone-related impurities/degradants, below the criteria or 50 µg/day TDI. Therefore, naloxone-related impurities/degradants specifications are acceptable at the (b) (4)% level for all proposed dosage forms.

In summary, it is noted that the buprenorphine-related impurities/degradants specification is (b) (4)% for only the lowest, (b) (4) mg buprenorphine dosage form. If (b) (4) are taken every day, the 50 µg/day TDI level would be exceeded. . However, the medical review team noted that a (b) (4) dose for a prolonged period of time is not likely. All the other dosage forms have a buprenorphine-related impurities/degradants specification of (b) (4)%. Therefore, the proposed specifications for naloxone-related impurities/degradants are acceptable for all proposed doses.

Drug Product Composition (inactive ingredient levels)

BEMA Buprenorphine NX uses BDSI's BioErodible MucoAdhesive (BEMA®) delivery technology comprised of flexible, water soluble polymeric films which adhere to the moist buccal mucosa and erode, so that there is no residual film to remove from the mucosa. The water soluble polymers and other excipients used in the BEMA delivery technology are listed in the FDA Inactive Ingredient Guide or certified as FDA/Flavor and Extract Manufacturers Association (FEMA) generally recognized as safe (GRAS). Novel Excipients would be those that are at levels that exceed approved levels regarding dose and duration for a relevant route of exposure. To this end, the excipients have been evaluated.

According to the Applicant's tables, no excipients are present in greater amounts than listed in the FDA's inactive ingredients lists (see tables on following pages). As discussed previously, the maximum recommended daily maintenance dose (MRDMD) for BNX would be 12.6/2.09 mg buprenorphine/naloxone compared to the Suboxone MRDMD of 24/6 mg. On this basis, the excipients levels in the following table need to be adjusted up by 100% from the highest 6.3/1.0444 mg disc dose to identify the daily dose of excipients from the entire disc at the MRDMD of BNX. These adjusted excipient levels will follow the drug product composition table.

BEMA[®] Buprenorphine NX Film Composition

Component	% w/w	Strength (mg Buprenorphine/naloxone free base)			
		(b) (4)	2.1/0.348	4.2/0.696	6.3/1.044
Purified Water ¹	-	-	-	-	
Buprenorphine Hydrochloride	3.456	(b) (4)	2.264	4.527	6.791
Propylene Glycol					(b) (4)
Sodium Benzoate					(b) (4)
Methylparaben					(b) (4)
Propylparaben					(b) (4)
Ferric Oxide, Yellow					(b) (4)
Citric Acid, (b) (4)					(b) (4)
Vitamin E Acetate					(b) (4)
Monobasic Sodium Phosphate, (b) (4)					(b) (4)
Polycarbophil					(b) (4)
Hydroxypropyl Cellulose					(b) (4)
Hydroxyethyl Cellulose					(b) (4)
Carboxymethylcellulose Sodium					(b) (4)
Sodium Hydroxide					(b) (4)
Dibasic Sodium Phosphate, (b) (4)					(b) (4)
Saccharin Sodium					(b) (4)
Citrus Blend Flavor					(b) (4)
Naloxone Hydrochloride	0.650	(b) (4)	0.425	0.850	1.275
(b) (4) Blue Ink					(b) (4)
Total Weight (mg)	100.00	(b) (4)	65.492	130.985	196.477

Following are the adjusted excipient composition levels (increase by 100% from the currently available highest disc dose) the BNX maximum recommended daily maintenance dose (MRDMD) of 12.6/2.09 mg buprenorphine/naloxone. Based on review of FDAs Inactive Ingredient Lists (public and proprietary) and the FDA's Integrity Product Master Data Base, all proposed single-component inactive ingredients are at allowable levels for chronic administration except for Vitamin E Acetate which will require further evaluation presented after this listing. In addition, Citrus Blend Flavor and (b) (4) Blue Ink will receive individual review after this listing as they consist of multiple components.

Total Daily Dose
Adjusted Excipient Levels (mg)

Propylene glycol	(b) (4)
Sodium Benzoate	(b) (4)
Methylparaben	(b) (4)
Propylparaben	(b) (4)
Ferric Oxide, Yellow	(b) (4)
Citric Acid, (b) (4)	(b) (4)
Vitamin E Acetate	(b) (4)
Monobasic Sodium Phosphate, (b) (4)	(b) (4)
Polycarbophil	(b) (4)
Hydroxypropyl Cellulose	(b) (4)
Hydroxyethyl Cellulose	(b) (4)

Carboxymethylcellulose sodium

Sodium Hydroxide

Dibasic Sodium Phosphate, (b) (4)

Saccharin Sodium

Citrus Blend Flavor

(b) (4) **Blue Ink**

=====

1. Vitamin E Acetate (b) (4) mg/day at MRDMD)
 - a. (b) (4) mg requested with no level approved except for (b) (4) contained in discontinued oral methyl testosterone (ANDA 84967)
 - b. Up to 1.34 mg vitamin E approved as an active ingredient in oral potassium chloride
 - c. Based on at rat LD50 of 3000 mg/kg and adding 5 safety factors of 10 to extrapolate to an allowable chronic human dose (based on USEPA Integrated Risk Information System method - IRIS) results in a daily dose of 1.8 mg/day
 - 1) Acute to subchronic dose; 2) subchronic to chronic dose; 3) animal to human; 4) human sensitive subpopulation; 5) additional safety factor for lack of data
 - d. As the excipient is not a structural alert (FDA CompTox consultation requested), the proposed level at the MRDMD is supported.
2. (b) (4) Blue Ink (b) (4) at MRDMD)
 - a. Contains ethanol, purified shellac, acetone, FD&C blue#1, ammonium hydroxide, & water
 - b. Classified by FDA as a color additive mixture, exempt from certification (21CFR 80.35(b) and 21 CFR 73.1).
 - c. All ingredients are GRAS or are specifically approved for use per FDA regulations
 - d. The lowest level of any other BNX excipient at the MRDMD is (b) (4) mg for sodium hydroxide. Assuming that (b) (4) is equal to NMT (b) (4) mg for the entire ink, all components are in approved chronic drugs at higher levels than (b) (4) mg
 - e. The ink is therefore at a supported level
3. Citrus Blend Flavor ((b) (4) mg/day at MRDMD) Listed in the FDA Inactive Ingredient Guide or certified as FDA/Flavor and Extract Manufacturers Association (FEMA) generally recognized as safe (GRAS) and also described under DMF (b) (4) (letter of authorization submitted) should support use of this flavor, but a risk assessment of the components was conducted by this reviewer. In the following table, with no apparent structural alerts, all chemicals constituents of the Citrus Blend Flavor (b) (4) /day potential dose at the MRDMD are acceptable for chronic dosing. Support for other components ((b) (4) /day) is described in comments column.

Citrus Blend Components - Total Dose Amount of Each Component at MRDMD of 8.4 mg
(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

There are no other impurities/degradants of concern that have not already been addressed. (see Drug Product in section 2.3 for a discussion of impurities/degradants specifications)

Container/Closure System - For the packaging, the product contact (b) (4)

and approved for food contact under 21CFR § Part 177 – Indirect Food Additives: Polymers Subpart B – Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces 177 (b) (4)

Extractables/Leachables - For this dry drug product, no extractables/leachables testing is required.

2.6 Proposed Clinical Population and Dosing Regimen

A single daily dose is recommended for opioid dependent patients. Proposed dosage forms are as follows (note that multiple discs may be required to achieve the desired maintenance dose):

BUNAVAIL™ (b) (4)

- this proposed dosage will not be approved based on CMC and/or ClinPharm issues (see those reviews for more details)

BUNAVAIL™ 2 mg (2.1 mg buprenorphine/0.348 mg naloxone)

BUNAVAIL™ 4 mg (4.2 mg buprenorphine/0.696 mg naloxone)

BUNAVAIL™ 6 mg (6.3 mg buprenorphine/1.044 mg naloxone)

The difference in bioavailability of Bunavail buccal compared to Suboxone sublingual tablet requires a different dosage strength to be administered to the patient. A Bunavail 4.2 mg buccal film roughly provides equivalent buprenorphine exposure to a Suboxone 8/2 mg sublingual tablet. The recommended maintenance human daily dose for Suboxone is 16/4 mg which based on buprenorphine exposure is roughly equivalent to the Bunavail dose of 8.4 mg buprenorphine. The MRDMD for Suboxone is 24/6 mg, with buprenorphine exposure comparable to 12.6/2 mg of BNX.

2.7 Regulatory Background

BDSI has developed BNX as three (3) component drug (BEMA, buprenorphine, and naloxone) starting with the preIND 110267 (submitted October 29, 2010) and the IND 110267 (original IND submitted March 18, 2011) with the intention of submitting a 505(b)(2) NDA using Suboxone sublingual tablets (NDA 20-733) as the reference drug. As such, BDSI has demonstrated “similar bioavailability” for buprenorphine and similar or lower systemic exposure to naloxone between BEMA Buprenorphine NX and Suboxone sublingual tablets.

3 Studies Submitted

3.1 Studies Reviewed

1. Determination of Buprenorphine and Norbuprenorphine in Beagle K2-EDTA Plasma by LC-MS-MS (study 02289JS)
2. 28-Day Buccal Toxicity Study of BEMA® Buprenorphine in Beagle Dogs (study 0436DB38.001)

3.2 Studies Not Reviewed – none (not including literature references)

3.3 Previous Reviews Referenced – IND 110267

4 Pharmacology (adapted from sponsor's submission)

4.1 Primary Pharmacology

Buprenorphine is a thebaine derivative and is a Schedule III controlled substance. Buprenorphine binds to μ -opioid, κ -opioid, δ -opioid, and opioid receptor-like 1 (ORL-1) receptors. The action of buprenorphine at these receptors has been well characterized, and buprenorphine is generally regarded as a μ -opioid receptor partial agonist and a κ -opioid receptor antagonist. Buprenorphine has a very slow rate of dissociation from μ -opioid receptor. The binding affinity order of buprenorphine to opioid receptors is $\mu > \delta > \kappa$. Despite its high binding affinity for κ -opioid receptors, buprenorphine exhibits low efficacy at this site, confirming it as a potent κ -opioid receptor antagonist.

Naloxone is a competitive antagonist of μ -opioid, κ -opioid, and δ -opioid receptors, with highest affinity for μ -opioid receptors. Naloxone has no opioid agonist activity. When naloxone is administered in usual doses in the absence of opioids, or in the absence of agonistic effects of other opioid antagonists, naloxone will exhibit no pharmacologic activity. When administered parenterally, naloxone will produce withdrawal symptoms in the presence of opioid dependence. However, due to the poor oral bioavailability of naloxone, systemic exposure is minimized upon oral administration.

4.2 Secondary Pharmacology

Buprenorphine has full analgesic efficacy in mouse models of acute somatic and visceral pain, persistent/chronic inflammatory pain and neuropathic pain. In parenteral doses, buprenorphine is 25 to 40-times more potent as an analgesic than morphine. Buprenorphine exerts its analgesic effect via high affinity binding to, and very slow rate of dissociation from μ -opioid receptors in the CNS. These properties may account for a long duration of action, the unpredictability of reversal by opioid antagonists, and a relatively low level of manifested physical dependence

4.3 Safety Pharmacology

Like other opioid receptor agonists, buprenorphine causes respiratory depression in animal models. In conscious rats, intravenous (IV) buprenorphine produced a nonlinear and modest effect on arterial concentration of CO₂ in plasma (PCO₂), with a ceiling effect at doses ≥ 1000 $\mu\text{g}/\text{kg}$, whereas fentanyl caused a larger degree of respiratory depression which was both linear and dose related. Buprenorphine can cause reductions in gastrointestinal transit time in rats and Naloxone can shift the buprenorphine dose-response curve to the right (i.e. requiring more buprenorphine for the same amount of effect).

5 Pharmacokinetics/ADME/Toxicokinetics

(adapted from sponsor's submission)

5.1 PK/ADME

The nonclinical pharmacokinetics of buprenorphine and naloxone by various routes of administration has been characterized. The pharmacokinetic properties of buprenorphine and naloxone in humans are presented in the Prescribing Information for Suboxone/Subutex sublingual tablets (NDAs 20-733/20-722) and are summarized in this section.

Buprenorphine is approximately 96% bound to plasma proteins, primarily to alpha and beta globulins. Naloxone is approximately 45% bound to plasma proteins, primarily to albumin. Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by the cytochrome P450 (CYP) 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation. Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group. Buprenorphine has a mean elimination half-life from plasma of 37 hours. Naloxone has a mean elimination half-life from plasma of 1.1 hours.

No nonclinical pharmacokinetic studies have been conducted with BEMA Buprenorphine NX. The pharmacokinetics of BEMA Buprenorphine (a similar product without naloxone) was evaluated as part of a 28-day, repeat dose toxicology study in Beagle dogs. Briefly, the 28-day, repeat dose toxicity study of BEMA Buprenorphine in dogs demonstrated good systemic exposure of buprenorphine with no systemic toxicity and no local irritation at the application site at a dose of buprenorphine in excess to that approved for Suboxone/Subutex.

5.2 Toxicokinetics

1. Determination of Buprenorphine and Norbuprenorphine in Beagle K2-EDTA Plasma by LC-MS-MS (GLP study 02289JS)

A bioanalytical LC-MS-MS method was developed for the determination of buprenorphine and norbuprenorphine in Beagle K2-EDTA plasma. The method was validated over the calibration range of 0.0125 to 5.00 ng/mL for buprenorphine and 0.0200 to 8.00 ng/mL for norbuprenorphine, based on the analysis of 0.500 mL of plasma. Acceptable accuracy, precision, linearity, and selectivity were demonstrated over the validated ranges for buprenorphine and norbuprenorphine. The stability of buprenorphine and norbuprenorphine in plasma after five freeze/thaw cycles and after approximately 122 hours storage at 22°C was established.

Analytical Methods and Validation Reports						
Species/ Sample Matrix	Analytes	Calibration Range	Type of Assay	Method Utilized	Noteworthy Findings (Precision and Accuracy Validation)	GLP Compliance
Dog (Beagle) / Plasma	Buprenorphine	0.0125 to 5.00 ng/mL in 0.50 mL plasma,	LC-MS-MS	ATM-1583 (Validation DCN 02289JS)	For QC samples from 0.0375 to 3.75 ng/mL buprenorphine, inter-run % bias ranged from -4.8 to 3.7 and inter-run %CV ranged from 3.1 to 4.5.	Yes
	Norbuprenorphine	0.0200 to 8.00 ng/mL in 0.50 mL plasma			For QC samples from 0.0600 to 6.00 mg/mL norbuprenorphine, inter-run % bias ranged from -2.5 to 4.2 and inter-run %CV ranged from 3.7 to 6.4.	

2. 28-Day Buccal Toxicity Study of BEMA® Buprenorphine in Beagle Dogs (GLP study 0436DB38.001)

In a 28-day study with BEMA buprenorphine in beagle dogs at 750 mcg administered 3 times per day to the same buccal site, PK values were determined (see table). The administered dose was the NOAEL with only anticipated pharmacological effects being observed and no buprenorphine-related local toxicity at the dosing site. These values are reported even though the safety of proposed doses for this IND are dependent on approved doses of buprenorphine in Suboxone and the relative bioavailability of buprenorphine in the proposed drug product compared to Suboxone.

Mean Buprenorphine and Norbuprenorphine Plasma Toxicokinetic Parameters for Beagle Dogs (Combined Genders) on Study Days 1 and 28

Parameter	Day 1	Day 28
Mean Buprenorphine Pharmacokinetic Parameters		
T _{max} (hr)	1.17	2.33
C _{max} (ng/mL)	44.8	28.8
AUC ₀₋₆ (hr*ng/mL)	84.51	47.27
AUC _{inf} (hr*ng/mL)	NA	92.59
T _½ (hr)	NA	5.89
Mean Norbuprenorphine Pharmacokinetic Parameters		
T _{max} (hr)	2.42	1.50
C _{max} (ng/mL)	1.17	1.11
AUC ₀₋₆ (hr*ng/mL)	2.666	2.696
AUC _{inf} (hr*ng/mL)	NA	7.085
T _½ (hr)	NA	9.23

NA = Not applicable

6 General Toxicology

6.1 Single-Dose Toxicity - none

6.2 Repeat-Dose Toxicity

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 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. Gender specific and combined TK data is 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 genders 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 genders suggesting possible increased metabolism.

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

Parameter	Treatment: BEMA Buprenorphine			
	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: 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	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: BEMA Buprenorphine			
	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.

7 Genetic Toxicology

N/A - 505(b)(2) to NDA 20-733 (Suboxone)

8 Carcinogenicity

N/A - 505(b)(2) to NDA 20-733 (Suboxone)

9 Reproductive and Developmental Toxicology

N/A - 505(b)(2) to NDA 20-733 (Suboxone)

10 Special Toxicology Studies

10.1 Local tolerance

No specific local tolerance studies of BEMA Buprenorphine NX have been conducted. A 28-day, repeat dose toxicology study in Beagle dogs was conducted (see section 6.1 for full review) which examined the local tolerance of the BEMA Buprenorphine disc (without naloxone). Dosing was 3-times daily to the same buccal application site at least 6 hours apart. No local irritation was observed at the application site which supports human safety for potential local effects of the BEMA disc as the size was similar to the proposed clinical drug product (each $\sim 3\text{cm}^2$) and was administered 3 times a day in the nonclinical study. However, the buprenorphine level as present in the nonclinical BEMA buprenorphine is $\sim 1/4$ the level (mg/cm^2) as in the proposed clinical drug product. On this basis, the potential local toxicity of the buprenorphine in the clinical drug product cannot be adequately assessed using the nonclinical study results.

11 Integrated Summary and Safety Evaluation

Introduction

This 505(b)(2) submission relies on safety information from Suboxone (NDA 20-733 – buprenorphine and naloxone sublingual tablet) and comparative bioavailability of Suboxone and BEMA Buprenorphine Naloxone (BNX). In addition, a 28-day dog study with BEMA buprenorphine was submitted to support clinical safety in regard to potential local toxicity with repeated applications of the BEMA disc with buprenorphine (no naloxone). Systemic exposure to buprenorphine was also assessed in the nonclinical

study. Of note is that based on preIND advice, we informed them no local toxicity study would be necessary if the to be marketed product established acceptable bioequivalence to Suboxone and local toxicity was adequately evaluated in clinical studies. This caveat from the preIND was demonstrated.

Bioavailability and Equivalent Dose levels

Comparable bioavailability of Suboxone and BNX has been demonstrated in clinical studies. The recommended daily maintenance dose (RDMD) or target dose of Suboxone for opioid dependence is 16/4 mg buprenorphine/naloxone as listed in the Suboxone label. This Suboxone dose is equivalent to a BNX dose of 8.4/1.4 mg buprenorphine/naloxone based on buprenorphine levels. However, the daily maintenance dose is generally in the range of 4/1 mg to 24/6 mg buprenorphine/naloxone per day depending on the individual patient. These Suboxone maintenance doses are equivalent to BNX doses of 2.1/0.35 to 12.6/2.09 mg buprenorphine/naloxone based on buprenorphine comparable bioavailability. Dosages higher than this have not been demonstrated to provide any clinical advantage as listed in the current Suboxone label. Therefore, the Suboxone human data supports the proposed BNX dosing allowing use of other nonclinical data related to buprenorphine and naloxone from Suboxone to be used in support of the BNX 505(b)(2) submission (e.g., reproductive toxicity, carcinogenicity, mutagenicity). In addition, the long-term use of approved, combined buprenorphine and naloxone sublingual tablets in Suboxone sufficiently supports the proposed combined dosing and long-term use of BNX.

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). Of note are the seventeen inactive ingredients in the drug product, two of which, (b)(4) Blue Ink (b)(4) and Citrus Blend Flavor (b)(4) mg) at the proposed of (b)(4) mg BNX contain 6 and (b)(4) additional inactive ingredients, respectively. Proposed chronic dosing with BNX containing these inactive ingredients was supported by being listed in the FDA Inactive Ingredient Guide, being certified as FDA/Flavor and Extract Manufacturers Association (FEMA) generally recognized as safe (GRAS), and/or by available toxicology information on the inactive ingredients in the literature.

Nonclinical Data and Safety Margins

The only nonclinical study submitted was a 28-day buccal dog study with BEMA buprenorphine in which the BEMA disc 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 0.808 mg buprenorphine/disc (~0.257 mg/cm²) and the BNX disc proposed for approval contains ~964 mg/cm² or ~3.8-fold more buprenorphine per cm² than in the nonclinically tested test article. While the dogs were dosed three times a day, based on these concentration differences, the local toxicity of buprenorphine in BEMA buprenorphine cannot be absolutely used to identify and assess potential local toxicity from BNX but it can for the potential local toxicity of BEMA. 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. Regardless, the data from the 28-day dog study can really only be used to compare systemic exposure of buprenorphine from BEMA buprenorphine to that for Suboxone and BNX. 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 Suboxone at the maximum recommended daily maintenance dose (MRDMD) of 24 mg buprenorphine and its bioequivalent dose of BNX of 12.6 mg buprenorphine that were obtained from clinical data for this NDA and extrapolated to the identified MRDMDs. Although not needed to support proposed human dosing because acceptable Suboxone and BNX bioavailability has been demonstrated, nonclinical support for the proposed human systemic exposure to buprenorphine from use of BNX exists. Human dosing is also supported for potential local toxicity of the BEMA disc alone.

Suboxone (tablet) and BEMA Buprenorphine NX (BNX) 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	Suboxone	24 ^a	8.76	84.49	NA	NA
	BNX	12.6 ^b	9.8	76.94	2.9	1.2
Dog ^c	BB	0.75 tid ^c	28.8	92.59	--	--

a - extrapolated from 8 mg dose (x3)

b - extrapolated from 6.3 mg dose (x2)

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

Summary

Based on nonclinical review of the information as listed above, NDA 205637 (Bunavail) may be approved with no other comments.

12 Appendix/Attachments - none

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

/s/

GARY P BOND
05/01/2014

ADAM M WASSERMAN
05/01/2014

I concur with Dr. Bond that the NDA may be approved from the nonclinical perspective.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205637

Applicant: BDSI
(BioDelivery Sciences International)

Stamp Date: August 7, 2013

Drug Name: BUNAVAIL™
(BEMA Buprenorphine NX)

NDA/BLA Type: 505(b)(2)
(Standard Priority)

Filing meeting: September 18, 2013
Filing date: August 7, 2013
PUDFA date: June 7, 2014

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		505(b)(2)-related studies (e.g., reproductive toxicity and carcinogenicity) have not been submitted but reference to approved product label for information has been submitted and is acceptable at present.
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		Nonclinical bridging study for local buccal toxicity conducted for the BioErodible MucoAdhesive (BEMA) Buprenorphine discs only, not to the to be marketed formulation containing naloxone (NX). Additional nonclinical studies could be necessary if clinical studies identify unacceptable local toxicity and/or systemic exposure in excess of the reference NDA exposures. No such condition(s) reported at this time by other reviewers based on current nonclinical query.
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		Administration route used in animal bridging study conducted by same route as intended human exposure route.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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

	Content Parameter	Yes	No	Comment
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		Container closer system for this solid drug product same as used for other, similar approved drugs. No issues at present time.
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		Dose ratios are listed as in referenced NDA 20-733 (Suboxone sublingual tablets). Proposed label will be amended as part of review to be consistent with other related buprenorphine product labels that are currently being standardized and also using "hybrid" PLR labeling format as new PLR regulation not final, unless it is finalized.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		No apparent impurity issues at present. Excipient levels must be in approved products at dose levels, duration of dosing, and comparable exposure route so that qualification is not required.
11	Has the applicant addressed any abuse potential issues in the submission?	X		Yes.
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.

NDA is fileable.

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

None.

Gary P. Bond, Ph.D. September 17, 2013
 Reviewing Pharmacologist Date

Adam M. Wasserman, Ph.D. September 17, 2013
 Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

GARY P BOND
09/17/2013

ADAM M WASSERMAN
09/17/2013