

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205637Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 14, 2014
From	Celia Winchell, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	205637
Applicant	BioDelivery Sciences International, Inc.
Date of Submission	August 7, 2013
PDUFA Goal Date	June 7, 2014
Proprietary Name / Established (USAN) names	BUNAVAIL (buprenorphine and naloxone) buccal film
Dosage forms / Strength	<ul style="list-style-type: none"> • (b)(4) mg buprenorphine/naloxone buccal film (not recommended for approval) • 2.1/0.35 mg buprenorphine/naloxone buccal film • 4.2/0.7 mg buprenorphine/naloxone buccal film • 6.3/1.04 mg buprenorphine/naloxone buccal film
Proposed Indication(s)	Maintenance treatment of opioid dependence
Recommended:	<i>Approval</i>

Contents

1. Introduction.....	3
2. Background.....	4
2.1 Role of Naloxone	5
2.2 Legal and Regulatory Issues Constraining Buprenorphine Treatment	6
3. CMC/Device	7
3.1 General product quality considerations	7
3.1.1. Drug Substances.....	7
3.1.2 Drug Product.....	8
3.1.3 Adhesion	9
3.1.4 Expiration Dating.....	9
3.1.5 Extraction Studies	10
3.2 Facilities review/inspection	10
3.3 Biowaiver Requests	10
4. Nonclinical Pharmacology/Toxicology	11
5. Clinical Pharmacology/Biopharmaceutics.....	12
5.1 General Background	12
5.2 Clinical Pharmacology Findings.....	13
5.2.1 Bioequivalence of Bunavail 4.2/0.7 mg to Reference Product.....	13
5.2.2 Data Supporting Other Doses	15
5.2.3 Effect of Beverages.....	16
5.3 QT assessment	16
6. Clinical Microbiology.....	16
7. Clinical/Statistical- Efficacy.....	17
8. Safety	20

9.	Advisory Committee Meeting.....	23
10.	Pediatrics.....	24
11.	Other Relevant Regulatory Issues.....	24
	11.2 Risk Evaluation and Mitigation Strategy.....	24
	11.3 OSI Inspection	25
	11.4 Cardiac Conduction Effects	25
	11.5 Financial Disclosures.....	26
	11. 5 Controlled Substances Staff Review.....	26
12.	Labeling	26
13.	Recommendations/Risk Benefit Assessment.....	27

1. Introduction

This application is for a new buprenorphine/naloxone combination product for the maintenance treatment of opioid dependence, referencing the approved product Suboxone (buprenorphine/naloxone) tablets (NDA 20733) through the 505(b)(2) pathway¹. The proprietary name, Bunavail, has been found acceptable.

Unlike Suboxone, which is a sublingual tablet, Bunavail uses a bioerosive mucosal adhesive (BEMA) technology for buccal delivery, a novel route for buprenorphine. Due to differences in bioavailability, the nominal doses are lower than those in Suboxone. Comparative pharmacokinetic studies have demonstrated exposure meeting criteria for bioequivalence using the 4.2/0.7 mg strength, and the application rests on the Agency's previous findings of safety and efficacy of Suboxone.

Four dosage strengths were proposed for marketing. These are:

- (b) (4) mg buprenorphine/naloxone (corresponds to 2/0.5 mg Suboxone tablet)
- 2.1/0.35 mg buprenorphine/naloxone (corresponds to 4/1 mg (two 2/0.5 mg) as Suboxone tablet)
- 4.2/0.7 mg buprenorphine/naloxone (corresponds to 8/2 mg Suboxone tablet)
- 6.3/1.04 mg buprenorphine/naloxone (corresponds to 12/3 mg (two 2/0.5 mg and one 8/2 mg as Suboxone tablet)

A comparative bioavailability study was performed comparing the 4.2/0.7 mg dose to the 8/2 mg Suboxone tablet. Biowaivers were sought for the higher and lower strengths, but the biowaiver for the lowest strength could not be granted. Therefore, only three strengths are recommended for approval.

Bunavail should be used in patients who have already begun treatment using buprenorphine-only sublingual products. The recommended dose is 8.4 mg buprenorphine (two 4.2/ (b) (4) mg films) as a single daily dose, but may be adjusted for the individual patient.

This review will briefly summarize the clinical pharmacology findings, safety findings from the pharmacokinetic studies in healthy, naltrexone-blocked volunteers, and findings from a clinical pharmacology study supporting the adequacy of the naloxone dose.

¹ Suboxone tablets have been withdrawn by the manufacturer, Reckitt Benckiser, from US marketing. However, the Agency has determined that Suboxone tablets were not withdrawn from sale for reasons of safety or effectiveness and the product is listed in the "Withdrawn Applications" section of the Orange Book.

2. Background

Buprenorphine is a partial agonist at the μ -opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain², two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence³, and a sublingual film formulation for opioid dependence⁴ and an extended-release transdermal film formulation for pain⁵ were approved in 2010.

Buprenorphine was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the μ -receptor. Like methadone, buprenorphine's activity at the μ -receptor was expected to relieve patients' urge to use illicit opioids, but like methadone, the long duration of action would allow patients to achieve a steady state, without the alternating highs and lows associated with opioid abuse that impair daily functioning. Additionally, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, further deterring abuse of these substances for buprenorphine-maintained patients.

Due to its partial agonist properties, the euphorogenic effects of buprenorphine are understood to reach a "ceiling" at moderate doses, beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists. This was expected to limit its attractiveness as a drug of abuse relative to full agonists.

Because it is a partial agonist, buprenorphine has the potential to precipitate withdrawal symptoms when used by an individual who is dependent on full opioid agonists such as heroin, methadone, or oxycodone. This product references the application for Suboxone, NDA 20733 (Reckitt Benckiser), a sublingual tablet formulation of buprenorphine that also contains naloxone. The naloxone is intended to be inactive when the product is used as intended, but to add an additional measure of abuse deterrence by precipitating more severe withdrawal if the product is crushed and injected by an individual dependent on full agonists.

The product was developed under IND 110267. BDSI originally met with the Division in a pre-IND meeting in January, 2011. At that time, they were advised that no clinical efficacy or safety data would be required, provided that the buprenorphine exposure was bioequivalent to the reference product. Regarding naloxone, the Applicant was advised that the naloxone exposure could be lower than the reference product when used as intended, but that they would need to provide information to show that the product would release sufficient naloxone under conditions of misuse to precipitate withdrawal in persons dependent on full agonist opioids. BDSI was also informed that additional safety data, collected in at least 200 patients for a minimum of 12 weeks, would need to be submitted addressing the potential for local toxicity.

² Buprenex, NDA 18401 Reckitt Benckiser

³ Subutex (buprenorphine sublingual tablets), NDA 20732 and Suboxone (buprenorphine/naloxone sublingual tablets), NDA 20733, Reckitt Benckiser

⁴ Suboxone (buprenorphine naloxone) film, NDA 22410, Reckitt Benckiser

⁵ Butrans, NDA 21306

2.1 Role of Naloxone

As noted above, although buprenorphine has the potential to precipitate withdrawal symptoms in individuals dependent on full agonists, naloxone was included in the Suboxone formulation with the aim of providing an additional measure of deterrence to intravenous misuse. The naloxone was intended to be inactive when the product is used as intended, sublingually. Some transmucosal absorption of naloxone is possible, however, and for this reason, it is recommended that patients transitioning from full opioids at the beginning of treatment be treated initially with a few days of a buprenorphine-only product (e.g. Subutex or generics). Because naloxone competes poorly with buprenorphine at the mu receptor, once a patient is maintained on buprenorphine, the combination product can be introduced.⁶ Naloxone is intended to produce aversive symptoms if the product is crushed and injected.

The current Agency approach to evaluating the abuse deterrent properties of drug products was not in place in 2002, when Suboxone tablets were approved. Because both buprenorphine and naloxone have the potential to precipitate withdrawal in opioid-dependent individuals, the contribution of naloxone to abuse-deterrence has not been definitively established. However, the referenced application provided evidence from laboratory studies that the amount of naloxone included in the formulation was capable of producing aversive effects when given in combination with buprenorphine. Ratios of (b)(4) 4:1, and (b)(4) (buprenorphine:naloxone) were evaluated and the 4:1 ratio was commercialized by Reckitt Benckiser. However, it is likely that even if the ratio were to be maintained, there are doses of naloxone which are too low to cause significant aversive effects.

During the IND stage, BDSI was told that as long as the naloxone exposure was no higher than in the reference product when used as intended, no safety or efficacy issues would arise. However, because of the increased bioavailability of the BDSI product compared to the reference product, the naloxone content would need to be reduced to yield plasma levels no higher than the reference when the product was used as intended. Therefore, information would be needed showing that the amount of naloxone in the final formulation was sufficient to produce an aversive effect under conditions of misuse. They sought and received comment on the study that they intended to use to provide this information and it was found acceptable.

⁶ Studies supporting the reference product, Suboxone, either used a buprenorphine-only sublingual solution (no naloxone at all in the study), or, in one study, introduced Suboxone after two days of Subutex. Therefore, the labeling recommends this approach. It is becoming more common in clinical practice to perform direct induction (treatment initiation) with Suboxone, and several sponsors of buprenorphine/naloxone combination products, including Orexo, are pursuing studies to show that Suboxone is as well-tolerated in initial use as Subutex. However, at this time, combination products are labeled for use after initial treatment with buprenorphine-only products.

2.2 Legal and Regulatory Issues Constraining Buprenorphine Treatment

Buprenorphine is a Schedule III Controlled Substance and physicians prescribing Buprenorphine must comply with the relevant aspects of the Controlled Substances Act. In addition, the provision of agonist treatment of opioid addiction is governed by certain legal requirements. Unlike methadone, buprenorphine may be prescribed by physicians meeting certain requirements.

Methadone treatment of opioid addiction is delivered in a closed distribution system (opioid treatment programs, OTPs) that originally required special licensing by both Federal and State authorities, under the Narcotic Addict Treatment Act of 1974. The current regulatory system is accreditation-based, but OTPs must still comply with specific regulations that pertain to the way clinics are run, the credentials of staff, and the delivery of care. To receive methadone maintenance, patients are required to attend an OTP, usually on a daily basis, with the possibility of earning the privilege of taking home doses as their treatment stability increases. Buprenorphine may also be administered to patients at OTPs.

Buprenorphine treatment is covered Title XXXV of the Children's Health Act of 2000 (P.L. 106-310), which provides a "Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment of Opioid-Dependent Patients." This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000). Under the provisions of DATA 2000, qualifying physicians may obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings. At present, the only products covered by DATA 2000 (i.e., Schedule III-IV, approved for the indication) are buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and films.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to necessary, concurrent psychosocial services. The 8 hour training courses are provided by various physician organizations (e.g. APA) and delivered in-person, in web-based formats, or through other mechanisms. Physicians who obtain DATA 2000 waivers may treat opioid addiction with products covered by the law in any appropriate clinical settings in which they are credentialed to practice medicine.

3. CMC/Device

The Chemistry review was conducted by Arthur Shaw, Ph.D.

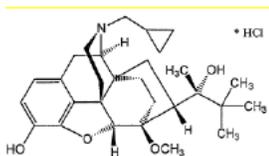
3.1 General product quality considerations

3.1.1. Drug Substances

The first drug substance is buprenorphine HCl, synthesized from thebaine and manufactured by (b) (4). It is then (b) (4). Complete CMC information is provided in DMF (b) (4) which was reviewed and found acceptable.

Molecular formula: $C_{29}H_{41}NO_4 \cdot HCl$

Molecular Weight: (b) (4) 504.1 (salt)

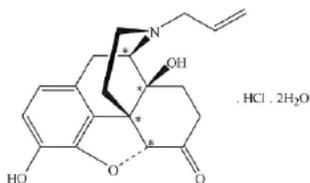


The buprenorphine drug substance is a white solid that is slightly soluble in water. It is (b) (4) to manufacture the drug product.

The second drug substance is naloxone HCl, manufactured by (b) (4). Complete CMC information is provided in DMF (b) (4) which was reviewed and found acceptable.

Molecular formula: $C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$

Relative molecular weight: 399.9



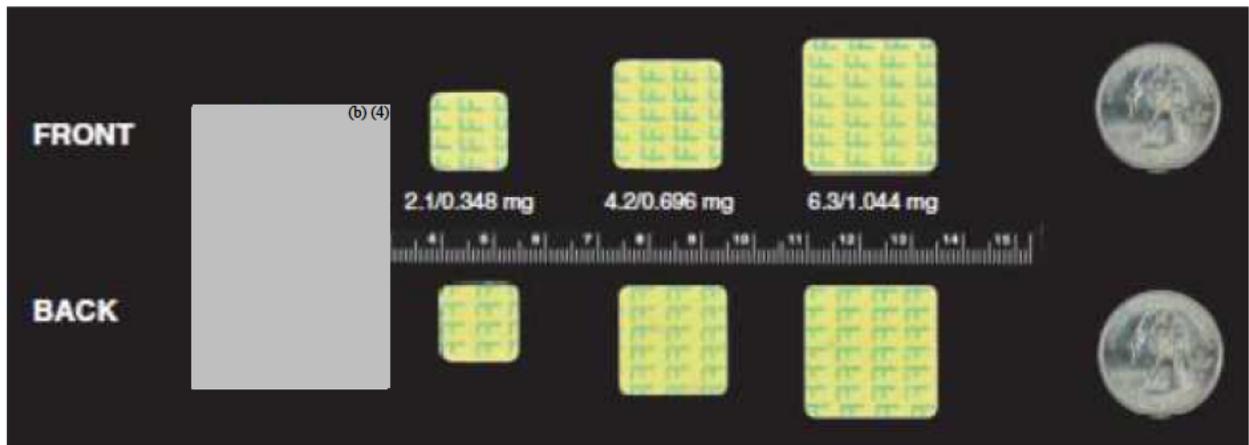
The naloxone drug substance is a white solid that is soluble in water. It is (b) (4) to manufacture the drug product.

3.1.2 Drug Product

The drug product is a polymeric film containing the drug substances in two layers. The mucoadhesive layer (ML) contains buprenorphine, while the backing layer BL contains naloxone.

The film is colored yellow and has the strength printed on the film, with the printing allowing the patient to see which side should be placed against the mucosa. The different strengths have the same relative compositions but are different sizes.

The illustration and below show the appearance and dimensions of the four strengths of Bunavail proposed by BDSI.



Although it is not possible to distinguish the front from the back in the photograph above, the applicant provided samples (placebo) and the review team determined that the printing is clearly legible, appearing reversed on the back side, and the patient will be able to tell which side is the correct side from the orientation of the numbers.

Approximate Dimensions of BEMA[®] Buprenorphine NX Films

Strength (mg)	Area (cm ²)	Length (mm)	Width (mm)
			(b) (4)
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

The two layers are (b) (4) but in the finished product they cannot be distinguished and the two layers cannot be peeled apart.

Dr. Shaw's review describes the manufacturing process as follows:

The manufacturing procedure involves the following unit steps:



Inactive ingredients include propylene glycol, polycarbophil, hydroxypropylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose, (b) (4), (b) (4), ink, flavoring (citrus) and (b) (4) (saccharine). All of the inactives are listed in the inactive ingredients database at levels above the levels in the drug product.

Dr. Shaw noted that the excipients were found to be compatible with the drug substances and that the manufacturing controls were adequate to achieve a reproducible product.

3.1.3 Adhesion

Dr. Shaw noted that although adhesion was tested, there was not a validated in vitro test for adhesion of the film to the mucosa. However, there was no evidence from the clinical data that lack of adhesion was a major problem. A tabulation of medication errors was provided, showing that issues relating to poor adhesion were reported by 6 (2%) of the participants in Study BNX-201. (See Dr. Horn's review.) Additionally, the formulation and manufacturing procedure are based on the Applicant's experience with the approved drug, Onsolis, a BEMA formulation of fentanyl (NDA 22266).

3.1.4 Expiration Dating

BDSI requested an expiration date of (b) (4) months based on extrapolation from 12-month data. However, the stability data can support only the twelve months because one of the parameters, an unidentified impurity, increases at both intermediate and accelerated storage conditions, which, Dr. Shaw notes, precludes extrapolation per ICH Q1E.

3.1.5 Extraction Studies

Although not required (because no claim of abuse deterrence other than the language already in the referenced label is proposed), BDSI performed a number of extraction studies as described in the FDA Guidance on development of abuse-deterrent opioids. The applicant compared Suboxone tablets with Bunavail films. Such studies were not performed when Suboxone tablets were under development nor when the Suboxone film product was developed. Various conditions and various media were used, with the objective of identifying methods that yielded differential extraction of buprenorphine and naloxone. The studies show that buprenorphine can be selectively extracted in (b) (4) from both Bunavail films and Suboxone tablets, leaving the naloxone behind and yielding a solution of buprenorphine dissolved in (b) (4). However, unlike the tablet, which disintegrates into the solution although the naloxone does not dissolve, the film remains intact and could be removed, taking the naloxone with it. It is noted, however, that there are also methods of separating the naloxone from buprenorphine in the reference tablet product.

3.2 Facilities review/inspection

Per Dr. Shaw's review, all inspections are satisfactory.

3.3 Biowaiver Requests

To support approval of the proposed product, BDSI conducted a bioequivalence study comparing the Bunavail 4.2/0.7 mg strength to the referenced 8/2 mg Suboxone sublingual tablet and conducted a relative bioavailability study between the 4.2/0.7 mg strength and the 6.3/1.04 mg strength to demonstrate dose proportionality. BDSI requested a waiver from conducting bioavailability/bioequivalence studies to support approval of the Bunavail film dosage strengths below 4.2/0.7 mg. The biowaiver request was reviewed by Kareen Riviere, Ph.D., supervised by Tapash Ghosh, Ph.D.

BDSI provided multi-point dissolution profile comparisons with f2 testing results for the lower two strengths versus the 4.2/0.7 mg strength using multi-media pHs. These data support a biowaiver for the 2.1/0.35 mg strength and not the (b) (4) mg strength.



Since the 4.2/0.696 mg strength was used in the pivotal BE study, the Applicant used this strength as the reference rather than the 6.3/1.044mg strength in the dissolution studies supporting the biowaiver for the lower strengths. This approach is acceptable.

(b) (4)

The data...demonstrate that the 2.1/0.348mg strength passes the f2 test when compared to the 4.2/0.696 mg strength in three media for buprenorphine. The Applicant did not provide the raw dissolution data for naloxone; therefore, this reviewer could not confirm the Applicant's f2 values. However, the naloxone dissolution profiles from the 2.1/0.35 mg and 4.2/0.7 mg appear nearly superimposable in all the dissolution media tested. Therefore, the dissolution profiles of the 2.1/0.348mg strength and 4.2/0.696 mg films are deemed similar.

(b) (4)

While it is highly unexpected that the dissolution profiles of proportionally similar films (b) (4) to be significantly different, the dissolution profile comparison data should not be undervalued or discounted in the biowaiver decision making process.

The provided data support a biowaiver for the 2.1/ 0.35 mg strength and not the (b) (4) mg strength. Thus, a biowaiver is granted for the 2.1/0.348 mg strength only. (b) (4)

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review was performed by Gary Bond, Ph.D., supervised by Adam Wasserman, Ph.D.

The only nonclinical study submitted was a 28-day study with in which BEMA buprenorphine film or placebo was administered to dogs using the same buccal site three times a day for 28 consecutive days. The study did not use the proposed drug product; there was no naloxone in the tested material. Additionally, the studied film contained approximately $\frac{1}{4}$ the buprenorphine per cm^2 found in the to-be-marketed product. Based on these concentration differences, the findings of the study are not informative with respect to the potential local toxicity of buprenorphine in the proposed product, but they do provide information about the potential local toxicity of excipients.

Known pharmacological effects of buprenorphine were observed. 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 a dose of 24 mg/day. Local toxicity noted for both groups was limited to minimal to slight cell infiltration of the oral mucosa. Dr.

Bond concluded that three repeated doses daily doses to the same buccal dose site did not result in any overt local toxicity.

In Dr. Bond’s 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 were identified.

In the label, text was added to sections describing non-clinical findings to link the exposure margins described in the existing text to the corresponding doses as delivered by Bunavail.

5. Clinical Pharmacology/Biopharmaceutics

5.1 General Background

This overview of buprenorphine and buprenorphine/naloxone clinical pharmacology is taken largely from the approved labeling for NDA 20-723 and 20-733.

Pharmacokinetics of buprenorphine and naloxone (as Suboxone) show wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability is low. Both C_{max} and AUC of buprenorphine show dose linearity in the range of 4 to 16 mg, but not dose proportionality. The table below from the labeling for Suboxone and Subutex shows the PK parameters. Buprenorphine has a mean elimination half-life of 37 hours; naloxone has a half-life of 1.1 hours. Naloxone does not affect the PK

Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8mg, and 16 mg Suboxone doses and 16mg Subutex dose (mean (%CV)).

Pharmacokinetic Parameter	Suboxone 4 mg	Suboxone 8 mg	Suboxone16 mg	Subutex 16 mg
C_{max} , ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC ₀₋₄₈ , hour.ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation. Cytochrome P-450 3A4 (CYP3A4) inhibitors may increase plasma concentrations of buprenorphine.

Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group. Buprenorphine is eliminated in urine (30%, primarily conjugated) and feces (69%, primarily free buprenorphine and norbuprenorphine).

Recently-reviewed data demonstrates that hepatic impairment differentially affects the PK of buprenorphine and naloxone. In subjects with mild hepatic impairment, the changes in mean C_{max} , AUC_{0-last}, and half-life values of both buprenorphine and naloxone are not clinically

significant and no dosing adjustment is needed in patients with mild hepatic impairment. However, in subjects with moderate and severe hepatic impairment, mean C_{max} , AUC_{0-last} , and half-life values of both buprenorphine and naloxone are increased, with the effects on naloxone being greater than that on buprenorphine. In patients with severe hepatic impairment, the increase in naloxone exposure is 10-fold or greater, and this could have implications for both safety and efficacy. Buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.

Renal impairment does not affect buprenorphine PK. The effects of renal failure on naloxone PK are unknown.

5.2 Clinical Pharmacology Findings

The clinical pharmacology review was conducted by Wei Qui, Ph.D., supervised by Yun Xu, Ph.D. The development program included a number of studies of dosages not ultimately proposed for marketing. However, because the various dosages (b) (4) the dose is proportional to the area of the pieces (b) (4). Of the doses proposed for marketing, only the 4.2/0.7 mg Bunavail has been directly compared to the reference product (in pivotal bioavailability study BNX-110).

5.2.1 Bioequivalence of Bunavail 4.2/0.7 mg to Reference Product

In Study BNX-110, Bunavail buccal film 4.2/0.7 mg was compared to both the reference product, Suboxone sublingual tablet 8/2 mg and to the Suboxone sublingual film 8/2 mg.

For buprenorphine, Bunavail buccal film 4.2/0.7 mg exhibited equivalent systemic exposure (C_{max} , AUC_{last} , and AUC_{inf}) in comparison to the listed drug, Suboxone sublingual tablet 8/2 mg.

For naloxone, Bunavail buccal film 4.2/0.7 mg had 27% lower naloxone C_{max} , 33% lower naloxone AUC_{last} , and 34% lower naloxone AUC_{inf} values in comparison to Suboxone sublingual tablet 8/2 mg.

Notably, as shown in the table below (reproduced in Dr. Qiu's review from the study report), the PK parameters do not show equivalent buprenorphine exposures between the Bunavail film and the Suboxone film, even though the Suboxone film and tablet have previously shown bioequivalence at the 8 mg dose. For this reason, reference to equivalent doses in the labeling will refer only to Suboxone tablet, and not (as the sponsor proposed) to (b) (4).

SUMMARY – CONCLUSIONS			
PHARMACOKINETICS RESULTS:			
Mean Plasma Pharmacokinetic Parameters			
Parameter	BEMA Buprenorphine NX film, containing 4.2/0.7 mg buprenorphine/naloxone	Suboxone sublingual tablet, containing 8/2 mg buprenorphine/naloxone	Suboxone sublingual film, containing 8/2 mg buprenorphine/naloxone
Mean (SD) Buprenorphine Pharmacokinetic Parameters			
	N = 65	N = 68	N = 70
T_{max} (h)	2.25 (0.75-4.00) ^a	1.50 (0.50-2.75) ^a	1.75 (0.50-3.05) ^a
C_{max} (ng/mL)	3.41 (1.26)	3.06 (1.28)	4.68 (2.07)
AUC_{last} (ng*h/mL)	25.75 (8.612)	26.98 (10.50)	36.72 (14.79)
AUC_{inf} (ng*h/mL)	27.17 (8.784)	28.67 (10.78)	38.38 (15.23)
AUC_{extrap} (%)	5.58 (3.12)	6.26 (3.98)	4.54 (2.56)
T_{1/2} (h)	27.53 (11.99)	28.67 (12.82)	31.71 (14.51)
T_{last} (h)	86.76 (30.52)	96.68 (31.82)	109.03 (29.94)
C_{last} (h)	0.0437 (0.0403)	0.0502 (0.0707)	0.0367 (0.0149)
Mean (SD) Norbuprenorphine Pharmacokinetic Parameters			
	N = 65	N = 68	N = 70
T_{max} (h)	2.25 (0.50-24.00) ^a	1.25 (0.50-24.00) ^a	1.25 (0.50-24.00) ^a
C_{max} (ng/mL)	0.529 (0.283)	1.27 (0.590)	1.32 (0.794)
AUC_{last} (ng*h/mL)	18.02 (8.608)	36.79 (16.19)	37.99 (17.37)
AUC_{inf} (ng*h/mL)	20.54 (8.658) ^b	39.88 (18.05)	41.64 (20.92)
AUC_{extrap} (%)	12.75 (13.33) ^b	7.20 (7.97)	8.01 (8.24)
T_{1/2} (h)	34.17 (13.38) ^b	32.64 (12.16)	34.77 (16.77)
T_{last} (h)	110.74 (35.94)	127.82 (28.69)	129.96 (24.70)
C_{last} (h)	0.0485 (0.0568)	0.0629 (0.127)	0.0572 (0.0480)
Mean (SD) Naloxone Pharmacokinetic Parameters			
	N = 65	N = 67	N = 69
T_{max} (h)	1.00 (0.50-2.00) ^a	0.75 (0.50-2.00) ^a	0.75 (0.25-1.50) ^a
C_{max} (ng/mL)	134 (69.7)	182 (89.1)	277 (129)
AUC_{last} (ng*h/mL)	333.5 (155.7)	488.3 (235.8)	693.6 (336.8)
AUC_{inf} (ng*h/mL)	340.5 (159.1)	505.8 (247.0)	709.1 (341.7)
AUC_{extrap} (%)	2.05 (1.03)	3.58 (3.01)	2.38 (2.27)
T_{1/2} (h)	2.37 (1.59)	4.93 (3.10)	4.83 (2.92)
T_{last} (h)	12.56 (4.29)	19.28 (5.99)	20.23 (5.78)
C_{last} (h)	2.03 (0.878)	2.53 (2.00)	2.39 (1.65)

a. Median (range) is reported for T_{max}

b. N = 64

5.2.2 Data Supporting Other Doses

BDSI submitted support for the additional proposed doses in the form of several PK studies of dose proportionality and dosage form equivalence, some of which used the final to-be-marketed film sizes and some of which did not. No studies used the proposed (b) (4) mg dose.

Study BNX-106

The dose-proportionality of buprenorphine and naloxone pharmacokinetics following single-dose administration of BEMA buprenorphine/naloxone film was assessed in 20 healthy subjects under naltrexone block in Study BNX-106. The study used the following doses (not the doses proposed for marketing):

- 0.875/0.15 mg
- 3.5/0.6 mg
- 5.25/0.9 mg

Each dose was administered as a single buccal film.

Dr. Qiu's review describes the results as follows:

Based on the power model, definitive dose proportionality of buprenorphine and naloxone PK parameters following the administration of BEMA Buprenorphine NX films (1 x 0.875/0.15 mg, 1 x 3.5/0.6 mg, and 1 x 5.25/0.9 mg) was not demonstrated over the buprenorphine dose range of 0.875 mg to 3.5 mg and naloxone dose range of 0.15 to 0.9 mg because the estimates of beta 1, the slopes of the power model, were significantly different from unity (1.0000). Buprenorphine and naloxone PK parameters (e.g., C_{max}, AUC₀₋₂₄, AUC_{last}, and AUC_{inf}) increased slightly less than proportional with dose over the buprenorphine dose range of 0.875 mg to 3.5 mg and naloxone dose range of 0.15 mg to 0.9 mg, respectively.

Study BNX-107

The relative bioavailabilities of buprenorphine and naloxone between two of the doses proposed for marketing were evaluated in 24 healthy subjects under naltrexone block in Study BNX-107. The study used the following doses:

- Bunavail 4.2/0.7 mg
- Bunavail 6.2/1.04 mg

Each dose was administered as a single buccal film.

This study demonstrated dose-proportionality between the two highest doses proposed for marketing. Dr. Qiu concluded:

Statistical analysis of the dose normalized log transformed C_{max}, AUC_{last} and AUC_{inf} between the 6.3/1.04 mg (1 x 6.3/1.04 mg) and 4.2/0.7 mg (1 x 4.2/0.7 mg) doses of BEMA Buprenorphine NX films found that the 90% CI for all PK parameters for both buprenorphine and naloxone were within the 80-125% range implies that the increase in buprenorphine and naloxone exposure is proportional to dose between the 4.2/0.7 mg and 6.3/1.04 mg BEMA Buprenorphine NX dose strengths.

This study provides support for the 6.3/1.04 mg dose.

Biowaivers were requested for the two lower doses. As noted above, the dissolution data submitted did not meet criteria for granting a biowaiver for the Bunavail 2.1/0.35 mg dose (b) (4)

5.2.3 Effect of Beverages

The PK program also included a study of the effects of co-administered liquids.

Dr. Qiu's review summarizes the results as follows:

Co-administration of low or high pH liquids lowered the C_{max} and AUC values of both buprenorphine and naloxone. The low pH fluid intake had the greater effect, with C_{max}, AUC_{last}, and AUC_{inf} values for buprenorphine being reduced by 59%, 52%, and 49%, respectively, compared to when no liquids were co-administered. The C_{max}, AUC_{last}, and AUC_{inf} values for naloxone were reduced by 76%, 74%, and 72%, respectively. The high pH fluid intake also reduced the systemic exposures of buprenorphine and naloxone. Buprenorphine C_{max}, AUC_{last}, and AUC_{inf} were reduced by 26%, 24%, and 24%, respectively, and naloxone C_{max}, AUC_{last}, and AUC_{inf} were reduced by 41%, 42%, and 40%, respectively. Caution language will be added to the label stating not to take the product with drink or food.

5.3 QT assessment

No QT assessment was undertaken in this development program.

Careful evaluation of the effects of buprenorphine on cardiac conduction was not performed during the development programs for Suboxone or Subutex. Based on *in vitro* binding studies, buprenorphine was not expected to have cardiac conduction effects. However, a thorough QT (TQT) study was performed in a more-recent development program for a transdermal buprenorphine product used for analgesia. In that study, a dose of 40 mcg/hour prolonged mean QT_c by a maximum of 9.2 (90% CI: 5.2-13.3) msec across the 13 assessment time points. This signal for QT prolongation was considered to meet the threshold for regulatory concern, but was not of clear clinical significance. The dose studied was significantly lower than the dose used for treating drug addiction; however, the potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval has not yet been evaluated in formal thorough QT studies. Such studies have been requested of Reckitt Benckiser as post-marketing requirements, but have not yet been completed. Sponsors of INDs to evaluate new formulations of buprenorphine, including BDSI, have been informed that TQT studies would be required for their NDAs, but could be performed post-approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

No new data on the clinical efficacy of buprenorphine were submitted.

The adequacy of the naloxone dose to perform as intended—that is, to cause aversive effects if the product is crushed and injected—was supported by a double-blind, placebo-controlled, four-treatment, four-period crossover study to determine the lowest dose of naloxone that would produce a withdrawal response when administered with buprenorphine in opioid-dependent subjects (Study LCR-04-01-01).

The design of the study is summarized in Dr. Horn's review and briefly described below:

Subjects with chronic moderate-to-severe non-cancer pain requiring at least 100 mg per day of oral morphine for at least 3 months were to continue to receive opioid at the same dose on the same schedule and receive four test articles administered intravenously (buprenorphine 0.75 mg; buprenorphine 0.75 mg + naloxone 0.1 mg; buprenorphine 0.75 mg + naloxone 0.2 mg; placebo) intended to induce withdrawal symptoms consecutively in random order, with three days between test articles to minimize any carryover effects. Withdrawal in response to the test articles was to be measured using the Clinical Opiate Withdrawal Scale, physiologic, and subject rated-measurements. The primary analysis comparing test articles was to be performed on the COWS scores.

To be eligible, subjects also had to display signs and symptoms of withdrawal (as evidenced by A COWS score of ≥ 5) in response to a challenge of naloxone, administered in 0.05 mg increments every five minutes until the target COWS was reached or a total of 0.2 mg had been administered.

Fifteen subjects enrolled and completed the study. There was no planned formal testing or sample size calculation.

Subjects had a mean age of 50 (range 24-63) and were 40% female. Baseline opioid use is summarized in the table below from Dr. Horn's review.

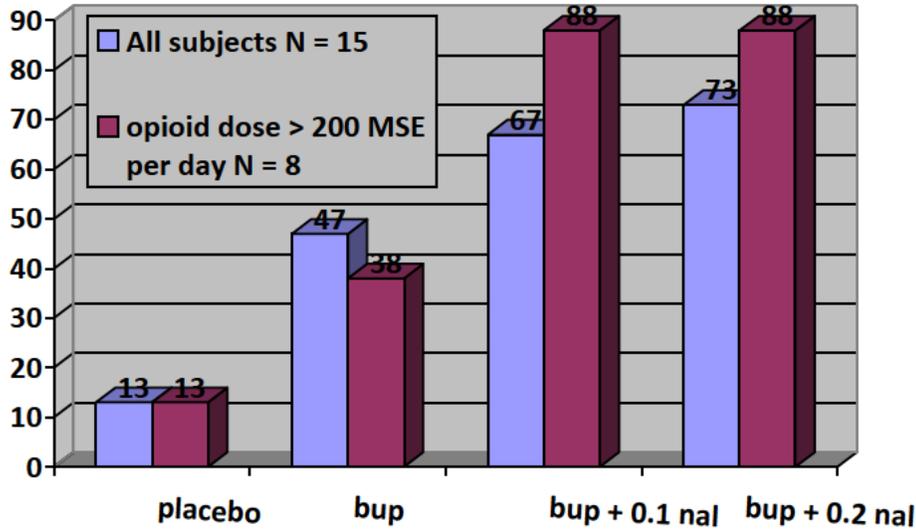
Subject ID	Opioid regimen	Total Daily Morphine Equivalent Dose (mg)
1002	Morphine and oxycodone	120
1003	Oxycodone	120
1005	Morphine and oxycodone	225
1006	Morphine and hydrocodone	90
1007	Fentanyl and oxycodone	587
1009	Morphine and oxycodone	100
1012	Oxycodone	300
1013	Methadone	1050
1015	Methadone	180
1016	Methadone	1260
1017	Morphine	420
1020	Morphine	520
1021	Morphine and hydrocodone	150
1023	Fentanyl and oxycodone	450
1024	Morphine	180

Source: CM dataset and CSR Table 6

Assessments included pharmacodynamics measures (COWS, Drug Effect Questionnaire, Opioid Agonist Scale) and physiologic measures, including vital signs and pupil diameter. Rescue treatment of withdrawal was protocol-specified to occur for COWS score >13. Many of the assessments were not recorded prior to rescue, and are therefore less meaningful to interpret. However, the proportion of subjects requiring rescue, and the mean COWS scores recorded prior to rescue, provide evidence that 0.1 mg and 0.2 mg naloxone was sufficient to precipitate withdrawal in most subjects.

Dr. Horn's review reproduces the following figure from the study report

Percentage of Subjects Requiring Rescue



This result is also consistent with the proportion of patients for whom an adverse event of withdrawal syndrome was reported (obscured somewhat by the division of these events between two system organ classes in the table below from Dr. Horn’s review).

AEs that occurred in more than one subject in any test article condition by PT

SOC	PT	Placebo	Bup	0.1 mg nal	0.2 mg nal
General disorders	Drug withdrawal syndrome	20%	13%	47%	67%
	Fatigue	0%	13%	7%	7%
Nervous System Disorders	Somnolence	20%	20%	7%	13%
	Headache	20%	0%	20%	13%
	Dizziness	13%	20%	0%	13%
Psychiatric Disorders	Withdrawal syndrome	0%	27%	13%	20%
Gastrointestinal Disorders	Nausea	0%	13%	0%	27%
Musculoskeletal and Connective Tissue Disorders	Back pain	0%	0%	7%	13%
	Myalgia	0%	0%	13%	0%

Source: CSR Table 14.3.1.2

Dr. Horn concluded:

The results in change from baseline in COWS scores support the effectiveness of buprenorphine and buprenorphine with naloxone at the two doses studied in causing clinically significant withdrawal in a substantial proportion of subjects. Naloxone appeared to worsen withdrawal symptoms in a dose-dependent fashion above what was observed with buprenorphine alone. The results on the COWS were supported by the trends observed in the physiological measures, even though many of the physiological measures were taken after rescue medication administration.

The COWS results are well-supported by the pattern of rescue medication use, which was administered based on COWS scores above 13 and indicated that subjects were experiencing withdrawal in a pattern consistent with the overall COWS data.

The subjects were on clinically relevant opioid maintenance doses in this study and the results can be reasonably be generalized to those with a physical dependence to full opioid agonists who would attempt to inject this product. Buprenorphine and naloxone in a ratio of 7.5 to 1 at a naloxone dose of 0.1 mg resulted in more withdrawal than buprenorphine alone, indicating that this ratio of buprenorphine to naloxone and this amount of naloxone is sufficient to increase the aversive effects of the product when injected. The amount of naloxone in the lowest [proposed] dose of the product is (b) (4), which is more than 0.1 mg and it is combined with (b) (4) mg buprenorphine in a 6:1 ratio, which is a lower ratio than the 7.5:1 ratio in the study.

8. Safety

Because this is a novel dosage form and route of administration for buprenorphine, a study evaluating local tolerability was conducted to address potential differences between the oral mucosal tolerability of Bunavail and the reference product. During development, BDSI was also advised that the oral mucosal evaluations in their tolerability study should be performed by dentists. However, they did not incorporate this advice. In subsequent discussions at the pre-NDA stage, the Division concluded that we were primarily concerned about symptomatic oral mucosal effects, and not those too subtle to be detected by a trained, but non-dentist, observer. The buccal mucosa is considered less vulnerable than the sublingual mucosa; therefore, although the route of administration is novel and some experience with the tolerability of the product is needed, there is considerable experience with transmucosal delivery of buprenorphine via a more vulnerable surface

Because the systemic exposure is the same as the reference product, the systemic safety of this product rests primarily on previous Agency findings for Suboxone.

Dr. Horn's review describes the study of local tolerability, Study BNX-201. It is briefly summarized here.

The study was a 12-week, open-label study in patients who had been maintained on Suboxone tablets at doses between 8 mg and 32 mg for at least 30 days, and who had no baseline abnormalities of buccal mucosa that could affect drug absorption. Based on the conversion scheme in the table below, patients were to be switched from Suboxone tablets to the BDSI buccal film as a single daily dose to be administered for 12 weeks. Dose adjustments could be made during the treatment period.

BNX-201 Conversion from Suboxone to buccal film

Current Suboxone tablet or film dose (buprenorphine/naloxone)	Initial BEMA Buprenorphine NX dose (size) (buprenorphine/naloxone) (b) (4)
8/2 mg	
12/3 mg	
16/4 mg	
24/6 mg	
32/8 mg	

Source: CSR Table 5

Doses requiring two films were to be administered with one film on each side of the mouth; for doses requiring more than two films, no more than two were to be applied on a single side. No regimens required more than four.

As is evident from the table above, the conversion ratio from Suboxone to buccal film is not the same conversion ratio proposed for marketing. This study appears to have been initiated based on incomplete information about the relative bioavailability of the products. The study drug, was, however, (b) (4) the same films that are used in the to-be-marketed product. Therefore the study drug and the to-be-marketed product differ only in the area of the films. The to-be-marketed films are larger. For example, the proposed dose that corresponds to an 8/2 mg dose of Suboxone, the 4.3/0.7 mg film, is 4.4 cm², (b) (4)% larger than the studied film.

Oral exams were to occur at Days 7, 14, 28, 56, and at the end of treatment (Day 84). Physician investigators were trained by a dentist to perform the exams and evaluated for proficiency in accordance with the Council of Interstate Testing Agencies for US dental licensure.

A total of 249 subjects were exposed to the BDSI film and evaluated for local tolerability.

Their mean age was 39 (range 20 – 62). Males comprised 66% of the study population. The mean dose of Suboxone at study entry was 16 mg per day with a range of 8 to 32 mg per day. The table below shows subject disposition. Over 79% of the subjects completed the study. Those who discontinued did so are described primarily using the vague terms “withdrew consent” and “other.” Dr. Horn’s review documents the circumstances of these withdrawals, which do not appear to be attributable to study drug-related adverse events.

BNX-201 Subject Disposition

Subject Disposition
All Subjects

	Total (N=249)
Safety Population	249 (100.0%)
Completed Study	197 (79.1%)
Discontinued	52 (20.9%)
Reasons for Discontinuation	
Adverse event	6 (2.4%)
Subject experiencing withdrawal symptoms	5 (2.0%)
Withdrew consent	16 (6.4%)
Lost to Follow-up	7 (2.8%)
Study terminated by sponsor	0
Other	18 (7.2%)

Source: CSR Table 14.1.1

Consistent with the subsequent finding that the dose conversion was too low by about 20%, many patients required dose increases during the study. Regardless of the dose of Suboxone the patients converted from, 30-40% required upward titration during the study, with the exception of the 8 patients converting from Suboxone 32/8 mg/day, who all required a dose increase. Only one subject had a dose decrease.

There were no deaths in the study or in the development program. There were two SAEs, one case of osteomyelitis and one case of suicidal ideation.

Adverse events that led to discontinuation were the two SAEs discussed above, headache, two positive urine toxicology screens and an oral ulcer in a subject whose urine was negative for buprenorphine.

The results of the oral mucosal examinations did not reveal any local toxicity concerns. Three subjects had mild mucosal redness during the study, which resolved without discontinuing treatment. Two subjects were observed to have swelling or raised lesions, which also resolved without discontinuing treatment. There was one subject with a mild mouth ulceration at the Day 7 visit. However, no buprenorphine or norbuprenorphine was detected in the subject's urine on Day 7, indicating that the subject was not taking the product.

Other treatment-emergent adverse events (occurring in more than two subjects) are shown in the table below from Dr. Horn's review. However, because this is an open-label study in patients already on buprenorphine, the findings are difficult to interpret. The most common event was drug withdrawal, attributable to the incorrect dose conversion scheme used in the study.

TEAEs Occurring in more than 2 Subjects

Adverse Event Preferred Term ^a	All Subjects N=249 n (%)
All Adverse Events	192 (77.1)
Drug Withdrawal Syndrome	89 (35.7)
Lethargy	22 (8.8)
Headache	20 (8.0)
Nasopharyngitis	14 (5.6)
Drug abuse	12 (4.8)
Fatigue	8 (3.2)
Upper Respiratory Tract Infection	8 (3.2)
Chills	7 (2.8)
Constipation	7 (2.8)
Toothache	7 (2.8)
Urinary Tract Infection	7 (2.8)
Back Pain	6 (2.4)
Drug Dependence	6 (2.4)
Hyperhidrosis	6 (2.4)
Insomnia	6 (2.4)
Viral Infection	6 (2.4)
Nausea	5 (2.0)
Anxiety	4 (1.6)
Gastroenteritis Viral	4 (1.6)
Hypertension	4 (1.6)
Oropharyngeal Pain	4 (1.6)
Sinusitis	4 (1.6)
Somnolence	4 (1.6)
Vomiting	4 (1.6)
Abdominal Pain	3 (1.2)
Asthenia	3 (1.2)
Bronchitis	3 (1.2)
Cough	3 (1.2)
Dermatitis Contact	3 (1.2)
Flushing	3 (1.2)
Influenza	3 (1.2)
Influenza-like Illness	3 (1.2)
Migraine	3 (1.2)
Oral Mucosal Erythema	3 (1.2)
Pain	3 (1.2)
Rhinorrhea	3 (1.2)

a. Source Data: Table 14.3.1.1.a, Table 14.3.1.2.a

Source: Table 20 BNX-201 CSR

There were no findings of concern in lab, vital sign, or EKG evaluations.

9. Advisory Committee Meeting

N/A

10. Pediatrics

BDSI requested a full waiver of the pediatric studies required under the Pediatric Research Equity Act (PREA). The justification provided was based on safety concerns in the neonatal age group, where buprenorphine may be used to treat symptoms of neonatal abstinence syndrome (NAS). Although there is increasing research interest in the use of buprenorphine for NAS, this product contains naloxone, which serves no purpose in the treatment of neonatal abstinence syndrome and might present a safety concern. Therefore, the Division agreed that a waiver in this age group was appropriate.

Waivers for Ages [REDACTED] ^{(b) (4)} to 16 years were requested on the grounds that studies would be impossible or highly impracticable, due to the low prevalence of opioid abuse and dependence.

The Division concurred that based on the most recent prevalence estimates and current and previous feasibility assessments, studies would be highly impracticable. This information was provided to the Pediatric Review Committee (PeRC), who agreed that a waiver should be granted.

11. Other Relevant Regulatory Issues

11.2 Risk Evaluation and Mitigation Strategy

Prior to market withdrawal, the reference product, Suboxone tablets, was marketed subject to a Risk Evaluation and Mitigation Strategy (REMS). Suboxone film continues to be marketed under the Suboxone/Subutex REMS. Although the REMS provisions under FDAAA call for a single shared system, a waiver was granted because Reckitt Benckiser declined to participate in a single shared system, and the Agency determined that the benefits of the waiver (access to medication) outweighed the burden of having multiple programs. All ANDA-holders are obliged to participate in the shared system, known as the BTOD (buprenorphine-containing transmucosal products for opioid dependence) REMS, but NDA holders are not subject to this requirement. One other NDA holder, Orexo, marketing Zubsolv buprenorphine/naloxone sublingual tablets under NDA 204242, joined the BTOD REMS at the time of approval of their application in 2012.

The Agency requested that BDSI join the shared system REMS to reduce the burden on the healthcare system by limiting the number of REMS for this class of products to two, and BDSI has arranged to do so.

The goals of the REMS are to:

1. Mitigate the risks of accidental overdose, misuse, and abuse
2. Inform patients of the serious risks associated with buprenorphine-containing products

REMS Elements:

1. Medication Guide
2. Elements to Assure Safe Use
 - Safe use Conditions
 - Monitoring
3. Implementation System
4. Timetable for Submission of Assessments

Materials for Prescribers:

1. Dear Prescriber Letter
2. Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers
3. Appropriate Use Checklist

Materials for Pharmacists:

1. Dear Pharmacist Letter
2. Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists

Materials for Patients:

1. Medication Guide

The materials have been updated to include a description of the Bunavail products, including a table showing the correspondence between Bunavail doses and Suboxone tablet doses.

For administrative reasons, the REMS materials approved for Bunavail will not include the information about hepatic effects, as the BTOD group will be concurrently modifying its REMS materials to include this information, and thus Bunavail's product information as well as the hepatic information can will be incorporated into the same modification. From a practical standpoint, materials will not actually be created or distributed without this information because the BTOD group will be immediately notified and the changes will be rapidly incorporated into the group's materials..

11.3 OSI Inspection

OSI's Division of Bioequivalence and GLP Compliance (DBGLPC) audited the clinical and analytical portions of Study BNX-110, the pivotal bioequivalence study and concluded that the data from the study were acceptable.

11.4 Cardiac Conduction Effects

BDSI was informed during the IND stage that a signal for QT prolongation meeting criteria for regulatory significance had been identified in a study of another buprenorphine product, at a dose significantly lower than the dose used for treating drug addiction. A study of the potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval has been requested of Reckitt Benckiser as post-marketing requirement (PMR), but has not yet been completed. BDSI was informed that a TQT study would be required for their NDA if the information was not available to be incorporated by reference at the time of submission, but that the study could be performed post-approval.

11.5 Financial Disclosures

Financial disclosures were reviewed by Dr. Horn who identified no concerns.

11.5 Controlled Substances Staff Review

BDSI did not seek new claims about abuse deterrence for Bunavail. The Controlled Substances team did not identify any concerns specific to the dosage form pertinent to abuse liability or abuse deterrence.

12. Labeling

The proprietary name, Bunavail, was found acceptable prior to NDA submission.

Physician labeling was based on the PLR version of the labeling for the reference product, which, in turn, was supported by studies of a formulation that was not ultimately marketed. Some aspects of labeling, as revised by the review team, were also based on recent literature reviews of the use of buprenorphine in pregnancy by the Maternal Health Team, and a recently-submitted study of the effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone which yielded important information relevant to safety. This material was not in the referenced product label when the NDA was submitted and therefore not included in the proposed label.

Key differences between the sponsor's proposed labeling and the labeling proposed by the review team include:

- References to the lowest strength were omitted because this strength was not recommended for approval (b) (4)
- Language describing the potential for precipitated withdrawal related to naloxone were revised to remove the statement that the symptoms are (b) (4) because at the dose of naloxone included in Bunavail, that the reaction is likely in most, but not all, individuals, and it may be aversive but not be particularly (b) (4).
- A new precaution regarding use of buprenorphine/naloxone combination products in patients with hepatic impairment was added.
- Based on a recent review of literature concerning the use of buprenorphine in pregnant and nursing women by the Maternal Health Team, revisions to the relevant sections of labeling have been made in other buprenorphine/naloxone product labels. These were incorporated into this label.
- (b) (4)
- In some places, the Applicant had inserted (b) (4) in text pertaining to scientific findings about the pharmacodynamics effects of sublingual administration. Because these studies were not conducted with (b) (4) administration, these references were removed.

-  (b) (4)
-
-

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval of three of the four proposed strengths.

The lowest strength is not recommended for approval because of a lack of information from either clinical studies or in vitro dissolution studies to support approval.

- Risk Benefit Assessment

This product provides the same systemic exposure to buprenorphine as the reference product, Suboxone tablets, and contains an amount of naloxone sufficient to produce aversive responses under conditions of intravenous misuse by many individuals with physical dependence on full opioid agonists. Its efficacy and benefit is expected to be the same as the reference product. It does not present new safety concerns compared to the reference product. It similarly does not provide any major safety benefits to patients, and will likely be subject to diversion, misuse, and abuse similar to the reference product. The unit-dose packaging could potentially prove advantageous in preventing accidental exposure. A REMS misuse, abuse, and accidental overdose will be needed to ensure the benefits outweigh the risks.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The components of the REMS are a MedGuide, ETASUs, and implementation system.

- Recommendation for other Postmarketing Requirements and Commitments

A TQT study of the effects of buprenorphine on cardiac conduction at doses used for addiction treatment should be required.

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

/s/

CELIA J WINCHELL
05/15/2014