Novel Buccal Film Formulation of Buprenorphine-Naloxone for the Maintenance Treatment of Opioid Dependence: A 12-Week Conversion Study

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ABSTRACT

Purpose: The purpose of this study was to provide a preliminary assessment of the safety, tolerability, symptom control, and acceptability of buprenorphine-naloxone buccal film (BBN) for the maintenance treatment of opioid dependence in patients converted from buprenorphine-naloxone sublingual tablet or film (SLBN), as well as to determine the conversion ratio for switching patients from SLBN to BBN.

Methods: This open-label study included adult opioid-dependent subjects stabilized on 8/2 to 32/8 mg/d of SLBN for a minimum of 30 days. Study subjects were converted to a bioequivalent dose of BBN and maintained for 12 weeks.

Findings: A total of 249 subjects (mean age 38.7 years, 65.9% male) were converted from SLBN to a single daily dose of BBN, and 79.1% completed the 12-week study. Adverse events and withdrawal symptoms led to discontinuation in 2.4% and 2.0% of BBN-treated subjects, respectively. Rates of constipation reported at baseline declined from 41% just before the initial BBN dose and within 24 hours of the last SLBN dose to 13% after 12 weeks of BBN treatment; treatment-emergent constipation was reported by 2.8% of BBN-treated subjects. Oral mucosal abnormalities were identified in 5% and 0.6% of systematic oral examinations in SLBN- and BBN-treated subjects, respectively. A total of 34 subjects had Clinical Opiate Withdrawal Scale total scores ranging from 10 to 25 (overall mean, 13.8) within 24 hours of taking their last SLBN dose, and scores for these subjects were reduced to a range of 0 to 3 (overall mean, 0.7) at 3 hours after the initial dose of BBN. Treatment compliance was high (108%); <1% of urine samples were buprenorphine-free, and 92.4% of BBN-treated subjects did not have a urine sample that tested positive for a non-prescribed opioid. A total of 91.3% subjects rated the taste of BBN as pleasant or neutral, and 82.5% rated BBN ease of use as easy or neutral. The overall mean final dose of BBN was 8.0/1.4 mg/d, yielding a 2:1 buprenorphine conversion ratio.

Implications: Although these results should be considered preliminary due to the open-label design, BBN was overall safe and well tolerated, and seemed to provide adequate symptom control, in the treatment of opioid-dependent subjects previously controlled on SLBN for a minimum of 30 days. There was good adherence to study medication and favorable patient acceptance of the buccal formulation. The SLBN/BBN buprenorphine conversion ratio was 2:1. ClinicalTrials.gov identifier: NCT01666119. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: buccal, buprenorphine, dependence, naloxone, opioid, safety.

INTRODUCTION

Opioid dependence is an important public health problem that is associated with significant morbidity and mortality.[1] In the United States, prescription opioid misuse has been described as an epidemic, with mortality now exceeding the combined rates for suicide and motor vehicle accidents, as well as the aggregate deaths from cocaine and heroin.[2] Physicians can treat their opioid-dependent patients with buprenorphine and fixed combinations of

Accepted for publication February 4, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.02.027
0149-2918/$ - see front matter

buprenorphine-naloxone (BN) in brand-name sublingual tablet and film formulations (SLBN)* and generic sublingual tablets. Despite evidence of their effectiveness,[3] the clinical utility of SLBN has been compromised by concerns about diversion, nonmedical use, and poor compliance with treatment.[4–7] Other concerns include challenges with palatability and tablet dissolution times,[6,8] which make it difficult for some patients to keep SLBN under their tongue, particularly when attempting to talk or swallow. In addition, talking while SLBN dissolves may affect the rate and extent of absorption.[9,10]

BN buccal film (BBN),† a novel transmucosal BN product, is a small, thin, bilayered dissolvable film that adheres to the buccal mucosa and uses Bio-Erodible MucoAdhesive (BEMA; BioDelivery Sciences International, Inc, Raleigh, North Carolina) drug delivery technology to optimize BN administration and patient convenience. BEMA delivery technology is composed of flexible water-soluble polymeric films. The mucoadhesive side contains the active ingredient buprenorphine and adheres to the moist buccal mucosa upon contact; the backing layer facilitates unidirectional buprenorphine absorption into the buccal mucosa, isolating the buprenorphine from saliva and limiting the amount of buprenorphine swallowed into the gastrointestinal tract. Because the film completely dissolves, there is no residual film to remove.

In pharmacokinetics (PK) research with the buccal formulation using BEMA technology, buprenorphine exposure was linear across doses of ~0.9, 3.5, and 5.25 mg, and the C_{max} and the AUC values for buprenorphine with a single 3.5/0.6–mg film were comparable to the equivalent dosage administered as four 0.875/0.15–mg films. These findings, which suggested that buprenorphine exposure with BBN 3.5/0.6 mg would be similar to SLBN 8/2 mg with no greater exposure to naloxone, provided the rationale for the conversion dose in the current study. Meanwhile, to determine the bioavailability of BBN 4.2/0.7 mg relative to SLBN 8/2–mg tablets and to demonstrate bioequivalent buprenorphine exposure and equal or lower naloxone exposure for BBN 4.2/0.7 mg relative to SLBN 8/2–mg tablets, an open-label, single-dose, crossover PK study in 80 healthy naltrexone-blocked volunteers was performed.[11] Buprenorphine exposure from BBN 4.2/0.7 mg was bioequivalent to an 8/2–mg SLBN tablet (Table I). Based on the comparable buprenorphine bioavailability and allowing for dosage adjustments, the current open-label study provides a preliminary assessment of the tolerability, symptom control, and patient acceptance with BBN and confirms the most appropriate conversion ratio between BBN and SLBN.

SUBJECTS AND METHODS

Subjects

This open-label study was approved by the Copernicus Group institutional review board on June 20, 2012, and was conducted between August 6, 2012, and January 8, 2013, at 10 study centers located in the United States. Study subjects included individuals diagnosed with opioid dependence according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*, who had been maintained on a stable daily dose (8–32 mg) of SLBN for a minimum of 30 days. Subjects were eligible for inclusion if they were adults aged 18 to 65 years (women of childbearing potential who were not pregnant or breastfeeding and were using an acceptable method of birth control) who had been diagnosed with opioid dependence or addiction in the past 12 months; had a positive urine buprenorphine and

Table I. Pharmacokinetic parameters for buprenorphine after use of 4.2/0.7–mg buprenorphine-naloxone buccal film (BBN) and 8/2–mg buprenorphine-naloxone sublingual tablet (SLBN).

Parameter	BBN 4.2/0.7 mg (n = 65)	SLBN Tablet 8/2 mg (n = 68)
T_{max}, h*	2.25 (0.75–4.00)	1.50 (0.50–2.75)
C_{max}, ng/mL	3.41 (1.26)	3.06 (1.28)
$AUC_{0-\infty}$, ng*h/mL	27.17 (8.784)	28.67 (10.78)
$t_{½}$, h	27.53 (11.99)	28.67 (12.82)

*Median (range). Unless otherwise indicated, values are given as mean (SD)

*Trademark: Suboxone® (Reckitt Benckiser plc, Parsippany, New Jersey).

†Trademark: Bunavail® (BioDelivery Sciences International, Inc, Raleigh, North Carolina).