

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BUNAVAIL safely and effectively. See full prescribing information for BUNAVAIL.

**BUNAVAIL (buprenorphine and naloxone) buccal film, CIII**  
**Initial U.S. Approval: 2002**

### INDICATIONS AND USAGE

BUNAVAIL is a partial opioid agonist indicated for the maintenance treatment of opioid dependence. Prescription use of this product is limited under the Drug Addiction Treatment Act. (1)

### DOSAGE AND ADMINISTRATION

Apply BUNAVAIL buccal film as a single daily dose. (2) The recommended daily dose for maintenance is 8.4 mg/1.4 mg.

### DOSAGE FORMS AND STRENGTHS

Buccal film: BUNAVAIL 2.1 mg buprenorphine/0.3 mg naloxone; BUNAVAIL 4.2 mg buprenorphine/0.7 mg naloxone and BUNAVAIL 6.3 mg buprenorphine/1 mg naloxone. (3)

### CONTRAINDICATIONS

Hypersensitivity to buprenorphine or naloxone. (4)

### WARNINGS AND PRECAUTIONS

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. (5.1)
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol). (5.2)
- Consider dose reduction of CNS depressants, BUNAVAIL buccal film, or both in situations of concomitant prescription. (5.3)
- Store BUNAVAIL buccal film safely and out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children. (5.4)
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome. (5.5)
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events. (5.6)
- Do not administer BUNAVAIL buccal film to patients with known hypersensitivity to buprenorphine or naloxone. (5.7)
- An opioid withdrawal syndrome is likely to occur with parenteral misuse of BUNAVAIL buccal film by individuals physically dependent on full opioid

agonists or by buccal administration before the agonist effects of other opioids have subsided. (5.8)

- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy. (5.9)
- BUNAVAIL buccal film is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a buprenorphine dose smaller than the lowest available BUNAVAIL strength. (5.10)
- Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment (5.11)
- Caution patients about the risk of driving or operating hazardous machinery. (5.12)

### ADVERSE REACTIONS

Adverse events commonly observed with administration of BUNAVAIL buccal films during clinical trials are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia and pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact (BioDelivery Sciences International) at 1-800-469-0261 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing. (7.1)
- Use caution in prescribing BUNAVAIL buccal film for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7.3)

### USE IN SPECIFIC POPULATIONS

- 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)
- Safety and effectiveness of BUNAVAIL buccal film in patients below the age of 16 has not been established. (8.4)
- Administer BUNAVAIL buccal film with caution to elderly or debilitated patients. (8.5)
- Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

## FULL PRESCRIBING INFORMATION: CONTENTS\*

1	INDICATIONS AND USAGE	5.9	Neonatal Withdrawal
2	DOSAGE AND ADMINISTRATION	5.10	Use in Opioid Naïve Patients
2.1	Maintenance	5.11	Use in Patients with Impaired Hepatic Function
2.2	Method of Administration	5.12	Impairment of Ability to Drive or Operate Machinery
2.3	Clinical Supervision	5.13	Orthostatic Hypotension
2.4	Patients With Hepatic Impairment	5.14	Elevation of Cerebrospinal Fluid Pressure
2.5	Unstable Patients	5.15	Elevation of Intraocular Pressure
2.6	Stopping Treatment	5.16	Effects in Acute Abdominal Conditions
2.7	Switching between SUBOXONE Sublingual Tablets or Films and BUNAVAIL buccal film	5.17	General Precautions
3	DOSAGE FORMS AND STRENGTHS	6	ADVERSE REACTIONS
4	CONTRAINDICATIONS	6.1	Adverse Events in Clinical Trials
5	WARNINGS AND PRECAUTIONS	7	DRUG INTERACTIONS
5.1	Abuse Potential	7.1	Cytochrome P-450 3A4 (CYP3A4) Inhibitors and Inducers
5.2	Respiratory Depression	7.2	Antiretrovirals
5.3	CNS Depression	7.3	Benzodiazepines
5.4	Unintentional Pediatric Exposure	8	USE IN SPECIFIC POPULATIONS
5.5	Dependence	8.1	Pregnancy
5.6	Hepatitis, Hepatic Events	8.3	Nursing Mothers
5.7	Allergic Reactions	8.4	Pediatric Use
5.8	Precipitation of Opioid Withdrawal Signs and Symptoms	8.5	Geriatric Use

8.6	Hepatic Impairment
8.7	Renal Impairment
9	DRUG ABUSE AND DEPENDENCE
9.1	Controlled Substance
9.2	Abuse
9.3	Dependence
10	OVERDOSAGE
11	DESCRIPTION
12	CLINICAL PHARMACOLOGY
12.1	Mechanism of Action
12.2	Pharmacodynamics

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12.3	Pharmacokinetics
13	NONCLINICAL TOXICOLOGY
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
16	HOW SUPPLIED/STORAGE AND HANDLING
17	PATIENT COUNSELING INFORMATION
17.1	Safe Use
17.2	Disposal of Unused

**\*Sections or subsections omitted from the full prescribing information are not listed.**

# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

BUNAVAIL buccal film is indicated for the maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

**Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.**

## 2 DOSAGE AND ADMINISTRATION

BUNAVAIL buccal film is applied to the buccal mucosa as a single daily dose. BUNAVAIL buccal film should be used in patients who have been initially inducted using buprenorphine sublingual tablets.

The difference in bioavailability of BUNAVAIL compared to SUBOXONE sublingual tablet requires a different dosage strength to be administered to the patient. A BUNAVAIL 4.2/0.7 mg buccal film provides equivalent buprenorphine exposure to a SUBOXONE 8/2 mg sublingual tablet.

Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits.

### 2.1 Maintenance

- BUNAVAIL buccal film is indicated for maintenance treatment. The recommended target dosage of BUNAVAIL buccal film is 8.4/1.4 mg per day as a single daily dose.
- The dosage of BUNAVAIL buccal film should be progressively adjusted in increments/decrements of 2.1/0.3 mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.
- The maintenance dose of BUNAVAIL buccal film is generally in the range of 2.1/0.3 mg buprenorphine/naloxone to 12.6/2.1 mg buprenorphine/naloxone per day depending on the individual patient. Dosages higher than this have not been demonstrated to provide any clinical advantage.

### 2.2 Method of Administration

The patient should:

- use the tongue to wet the inside of the cheek or rinse the mouth with water to moisten the area immediately before placement of BUNAVAIL;
- open the BUNAVAIL package immediately prior to use as indicated by the instructions;
- hold the BUNAVAIL film with clean, dry fingers with the text (BN2, BN4, or BN6) facing up;
- place the side of the BUNAVAIL film with the text (BN2, BN4, or BN6) against the inside of the cheek;
- press and hold the film in place for 5 seconds.

BUNAVAIL film(s) adheres to the moist buccal mucosa and should stay in place after this period.

If multiple films need to be administered, the patient should immediately apply the next film according to the steps above. Note that when two films are required for one dose, the patient should place one film on the inside of one cheek and the other film on the inside of the other cheek. For doses requiring multiple films, no more than two films should be applied to the inside of one cheek at a time.

BUNAVAIL film(s) completely dissolves after application. The patient should be instructed to avoid manipulating the film(s) with the tongue or finger(s) and avoid drinking or eating food until the film(s) dissolves. BUNAVAIL film should not be chewed or swallowed as this may result in lower peak concentrations and lower bioavailability [see *Clinical Pharmacology (12.3)*].

Instruct the patient to use the entire film. BUNAVAIL should not be cut or torn.

**Proper administration technique should be demonstrated to the patient.**

## 2.3 Clinical Supervision

Treatment should be initiated with supervised administration, progressing to unsupervised administration as the patient's clinical stability permits. BUNAVAIL buccal film is subject to diversion and abuse. When determining the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.

Ideally patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient progress.

Once a stable dosage has been achieved and patient assessment (e.g., urine drug screening) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of medication who are making progress toward their treatment objectives. Continuation or modification of pharmacotherapy should be based on the physician's evaluation of treatment outcomes and objectives such as:

1. Absence of medication toxicity
2. Absence of medical or behavioral adverse effects
3. Responsible handling of medications by the patient
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities)
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use)

If treatment goals are not being achieved, the physician should re-evaluate the appropriateness of continuing the current treatment.

## **2.4 Patients With Hepatic Impairment**

Because the doses of this fixed combination product cannot be individually titrated, severe hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine, and moderate hepatic impairment also results in a reduced clearance of naloxone to a greater extent than buprenorphine, the combination product should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment [see *Warnings and Precautions* (5.11)].

## **2.5 Unstable Patients**

Physicians will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention such that the physician does not feel that he/she has the expertise to manage the patient. In such cases, the physician may want to assess whether to refer the patient to a specialist or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

## **2.6 Stopping Treatment**

The decision to discontinue therapy with BUNAVAIL buccal film after a period of maintenance should be made as part of a comprehensive treatment plan. Taper patients to avoid opioid withdrawal signs and symptoms.

## 2.7 Switching between SUBOXONE Sublingual Tablets or Films and BUNAVAIL buccal film

The difference in bioavailability of BUNAVAIL compared to SUBOXONE sublingual tablet requires a different dosage strength to be administered to the patient. A BUNAVAIL 4.2/0.7 mg buccal film provides equivalent buprenorphine exposure to a SUBOXONE 8/2 mg sublingual tablet.

Patients being switched between SUBOXONE dosage strengths and BUNAVAIL dosage strengths should be started on the corresponding dosage as defined below:

Suboxone Sublingual Tablet Dosage Strength	Corresponding BUNAVAIL Buccal Film Strength
4/1 mg buprenorphine/naloxone	2.1/0.3 mg buprenorphine/naloxone
8/2 mg buprenorphine/naloxone	4.2/0.7 mg buprenorphine/naloxone
12/3 mg buprenorphine/naloxone	6.3/1 mg buprenorphine/naloxone

## 3 DOSAGE FORMS AND STRENGTHS

BUNAVAIL buccal film is supplied as a yellow rectangular buccal film in three dosage strengths:

- buprenorphine/naloxone 2.1 mg / 0.3 mg
- buprenorphine/naloxone 4.2 mg / 0.7 mg
- buprenorphine/naloxone 6.3 mg / 1 mg

## 4 CONTRAINDICATIONS

BUNAVAIL buccal film should not be administered to patients who have been shown to be hypersensitive to buprenorphine or naloxone as serious adverse reactions, including anaphylactic shock, have been reported [see *Warnings and Precautions (5.7)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Abuse Potential

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. Prescribe and dispense buprenorphine with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the home. Clinical

monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits [see *Drug Abuse and Dependence (9.2)*].

## 5.2 Respiratory Depression

Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with BUNAVAIL buccal film [see *Drug Interactions (7.3)*].

**In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.**

BUNAVAIL buccal film should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

## 5.3 CNS Depression

Patients receiving buprenorphine in the presence of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression. Consider dose reduction of CNS depressants, BUNAVAIL buccal film, or both in situations of concomitant prescription [see *Drug Interactions (7.3)*].

## 5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children and destroy any unused medication appropriately [see *Patient Counseling Information (17.2)*].

## 5.5 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon

abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion [see *Drug Abuse and Dependence* (9.3)].

## **5.6 Hepatitis, Hepatic Events**

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, BUNAVAIL buccal film may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

## **5.7 Allergic Reactions**

Cases of hypersensitivity to buprenorphine and naloxone containing products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives and pruritus. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to the use of BUNAVAIL buccal film.

## **5.8 Precipitation of Opioid Withdrawal Signs and Symptoms**

Because it contains naloxone, BUNAVAIL buccal film is likely to produce withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Because of the partial agonist properties of buprenorphine, BUNAVAIL buccal film may precipitate opioid withdrawal signs and symptoms in such persons if administered buccally before the agonist effects of the opioid have subsided.



## **5.9 Neonatal Withdrawal**

Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal signs ranged from Day 1 to Day 8 of life with most cases occurring on Day 1. Adverse events associated with the neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus, and there have been reports of convulsions, apnea, respiratory depression, and bradycardia.

## **5.10 Use in Opioid Naïve Patients**

There have been reported deaths of opioid naïve individuals who received a 2 mg dose of buprenorphine, smaller than the lowest strength of BUNAVAIL, for analgesia. BUNAVAIL buccal film is not appropriate as an analgesic.

## **5.11 Use in Patients with Impaired Hepatic Function**

Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. Because hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine, the doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated. Therefore, patients with severe hepatic impairment will be exposed to substantially higher levels of naloxone than patients with normal hepatic function. This may result in an increased risk of precipitated withdrawal at the beginning of treatment (induction) and may interfere with buprenorphine's efficacy throughout treatment. In patients with moderate hepatic impairment, the differential reduction of naloxone clearance compared to buprenorphine clearance is not as great as in subjects with severe hepatic impairment. Therefore, buprenorphine/naloxone products are not recommended for initiation of treatment (induction) in patients with moderate hepatic impairment due to the increased risk of precipitated withdrawal. However, buprenorphine/naloxone products may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone. However, patients should be carefully monitored and consideration given to the possibility of naloxone interfering with buprenorphine's efficacy [see *Use in Specific Populations* (8.6)].

## **5.12 Impairment of Ability to Drive or Operate Machinery**

BUNAVAIL buccal film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that BUNAVAIL buccal film therapy does not adversely affect his or her ability to engage in such activities.

### **5.13 Orthostatic Hypotension**

Like other opioids, BUNAVAIL buccal film may produce orthostatic hypotension in ambulatory patients.

### **5.14 Elevation of Cerebrospinal Fluid Pressure**

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

### **5.15 Elevation of Intrahepatic Pressure**

Buprenorphine has been shown to increase intrahepatic pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

### **5.16 Effects in Acute Abdominal Conditions**

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

### **5.17 General Precautions**

BUNAVAIL buccal film should be administered with caution in debilitated patients and those with myxedema or hypothyroidism, adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

## **6 ADVERSE REACTIONS**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### **6.1 Adverse Events in Clinical Trials**

The safety of BUNAVAIL buccal film is supported by clinical trials using buprenorphine and naloxone sublingual tablets, and other trials using buprenorphine tablets and buprenorphine sublingual solutions, as well as an open-label study in 249 patients treated with BUNAVAIL buccal film. In total, safety data from clinical studies are available from over 3000 opioid-dependent subjects exposed to buprenorphine at doses in the range used in the treatment of

opioid addiction. Few differences in the adverse event profile were noted among buprenorphine and naloxone sublingual tablets, buprenorphine sublingual tablets and a buprenorphine ethanolic sublingual solution.

The safety and tolerability of BUNAVAIL was evaluated in a 12-week clinical study of BUNAVAIL in 249 opioid-dependent subjects stabilized on buprenorphine and naloxone sublingual tablet or film dosages of buprenorphine 8-32 mg/day.

The following adverse reactions were reported to occur by at least 5% of patients in a 12-week study with BUNAVAIL: drug withdrawal syndrome, lethargy and headache.

The adverse reactions listed below represent those that were reported by >1%, but less than 5% of patients from the 12-week clinical trial while receiving BUNAVAIL. Events are classified by system organ class.

- **General disorders and administration site conditions:** fatigue and chills
- **Nervous system disorders:** somnolence
- **Psychiatric disorders:** drug dependence and insomnia
- **Gastrointestinal disorders:** constipation and oral mucosal erythema
- **Respiratory, thoracic and mediastinal disorders:** rhinorrhea
- **Skin and subcutaneous tissue disorders:** hyperhidrosis

The following adverse events were reported to occur by at least 5% of patients in a 4-week study with buprenorphine and naloxone sublingual tablets ([Table 1](#)).

**Table 1**

**Adverse Events (≥ 5%) by Body System and Treatment Group in a 4-week Study**

<b>Body System/ Adverse Event (COSTART) Terminology</b>	<b>Buprenorphine/naloxone sublingual tablets 16/4 mg/day N=107 n (%)</b>	<b>Placebo N=107 n (%)</b>
<b>Body as a Whole</b>		
Asthenia	7 (6.5%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.5%)
Headache	39 (36.4%)	24 (22.4%)
Infection	6 (5.6%)	7 (6.5%)
Pain	24 (22.4%)	20 (18.7%)
Pain abdomen	12 (11.2%)	7 (6.5%)
Pain back	4 (3.7%)	12 (11.2%)
Withdrawal syndrome	27 (25.2%)	40 (37.4%)
<b>Cardiovascular System</b>		
Vasodilation	10 (9.3%)	7 (6.5%)
<b>Digestive System</b>		
Constipation	13 (12.1%)	3 (2.8%)
Diarrhea	4 (3.7%)	16 (15.0%)
Nausea	16 (15.0%)	12 (11.2%)
Vomiting	8 (7.5%)	5 (4.7%)

<b>Nervous System</b>		
Insomnia	15 (14.0%)	17 (15.9%)
<b>Respiratory System</b>		
Rhinitis	5 (4.7%)	14 (13.1%)
<b>Skin and Appendages</b>		
Sweating	15 (14.0%)	11 (10.3%)

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of buprenorphine solutions, over a range of doses in four months of treatment. [Table 2](#) shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled study.

**Table 2**

**Adverse Events (> 5%) by Body System and Treatment Group in a 16-week Study**

Body System /Adverse Event (COSTART Terminology)	Buprenorphine Dose*				
	Very Low* (N=184) n (%)	Low* (N=180) n (%)	Moderate* (N=186) n (%)	High* (N=181) n (%)	Total* (N=731) n (%)
<b>Body as a Whole</b>					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu Syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury Accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain Back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal Syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
<b>Digestive System</b>					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
<b>Nervous System</b>					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
<b>Respiratory System</b>					
Cough Increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
<b>Skin and Appendages</b>					

Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
<b>Special Senses</b>					
Runny Eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)
*Sublingual solution. Doses in this table cannot necessarily be delivered in film form, but for comparison purposes: “very low” dose (1 mg solution) would be less than a tablet dose of 2 mg; “low” dose (4 mg solution) approximates a 6 mg tablet dose; “moderate” dose (8 mg solution) approximates a 12 mg tablet dose; “high” dose (16 mg solution) approximates a 24 mg tablet dose.					

## 7 DRUG INTERACTIONS

### 7.1 Cytochrome P-450 3A4 (CYP3A4) Inhibitors and Inducers

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when BUNAVAIL buccal film is given concurrently with agents that affect CYP3A4 activity. The concomitant use of BUNAVAIL buccal film with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents.

The interaction of buprenorphine with CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving BUNAVAIL buccal films be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered [see *Clinical Pharmacology* (12.3)].

### 7.2 Antiretrovirals

Three classes of antiretroviral agents have been evaluated for CYP3A4 interactions with buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine and etravirine are known CYP3A4 inducers whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamics effects. It is recommended that patients who are on chronic buprenorphine treatment have their dose monitored if NNRTIs are added to their treatment regimen. Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetics and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. Monitoring of patients taking buprenorphine and atazanavir with and without ritonavir is recommended, and dose reduction of buprenorphine may be warranted.

### **7.3 Benzodiazepines**

There have been a number of post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines. In many, but not all of these cases, buprenorphine was misused by self-injection. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual clinical ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. BUNAVAIL buccal films should be prescribed with caution to patients taking benzodiazepines or other drugs that act on the CNS, regardless of whether these drugs are taken on the advice of a physician or are being abused/misused. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking BUNAVAIL buccal film, and should also be cautioned to use benzodiazepines concurrently with BUNAVAIL buccal films only as directed by their physician.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C.

#### *Risk Summary*

There are no adequate and well-controlled studies of BUNAVAIL buccal film 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 postnatal 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 rabbits.

BUNAVAIL buccal film should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### *Clinical Considerations*

##### *Disease-associated maternal and embryo-fetal risk*

Opioid dependence in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death.

##### *Fetal/neonatal adverse reactions*

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 *Warnings and Precautions (5.9)*].

### *Labor or Delivery*

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.

### *Data*

#### *Human Data*

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 to be a dose-response relationship.

#### *Animal Data*

BUNAVAIL has been shown to have differences in bioavailability compared to buprenorphine/naloxone-containing sublingual products. The exposure margins listed below are based on body surface area comparisons ( $\text{mg}/\text{m}^2$ ) to the recommended human sublingual dose of 16 mg buprenorphine from Suboxone, which is equivalent to the recommended human buccal dose (RHD) of 8.4 mg buprenorphine from BUNAVAIL.

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 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 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).

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis). Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the RHD), 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).

### **8.3 Nursing Mothers**

#### **Risk Summary**

Based on two studies in 13 lactating women, buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have not shown adverse reactions in breastfed infants. There are no data on the combination product buprenorphine/naloxone in breastfeeding, however oral absorption of naloxone is minimal. Caution should be exercised when BUNAVAIL is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BUNAVAIL and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

#### **Clinical Considerations**

Advise the nursing mother taking BUNAVAIL to monitor the infant for increased drowsiness and breathing difficulties.

#### **Data**

Based on limited data from a study of 6 lactating women who were taking a median oral dose of buprenorphine of 0.29 mg/kg/day 5-8 days after delivery, breast milk contained a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, which are equal to 0.2% and 0.12% of the maternal weight-adjusted dose.

Based on limited data from a study of 7 lactating women who were taking a median oral dose of buprenorphine of 7 mg/day an average of 1.12 months after delivery, the mean milk concentrations of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L respectively. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, which are 0.38% and 0.18% of the maternal weight-adjusted dose.



No adverse reactions were observed in the infants in these two studies.

#### **8.4 Pediatric Use**

The safety and effectiveness of BUNAVAIL buccal films have not been established in pediatric patients.

This product is not appropriate for the treatment of neonatal abstinence syndrome in neonates, because it contains naloxone, an opioid antagonist.

#### **8.5 Geriatric Use**

Clinical studies of BUNAVAIL buccal films did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

#### **8.6 Hepatic Impairment**

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone has been evaluated in a pharmacokinetic study. Both drugs are extensively metabolized in the liver. While no clinically significant changes have been observed in subjects with mild hepatic impairment; the plasma levels have been shown to be higher and half-life values have been shown to be longer for both buprenorphine and naloxone in subjects with moderate and severe hepatic impairment. The magnitude of the effects on naloxone is greater than that on buprenorphine in both moderately and severely impaired subjects. The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than in subjects with moderate hepatic impairment, and therefore the clinical impact of these effects is likely to be greater in patients with severe hepatic impairment than in patients with moderate hepatic impairment. Buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment [see *Warnings and Precautions* (5.11) and *Clinical Pharmacology* (12.3)].

#### **8.7 Renal Impairment**

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine. The effects of renal failure on naloxone pharmacokinetics are unknown.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

**Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.**

### 9.2 Abuse

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The physician may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal requests of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication are appropriate measures that help to limit abuse of opioid drugs.

### 9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset [see *Warnings and Precautions (5.5)*].

A neonatal withdrawal syndrome has been reported in the infants of women treated with buprenorphine during pregnancy [see *Warnings and Precautions (5.9)*].

## 10 OVERDOSAGE

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

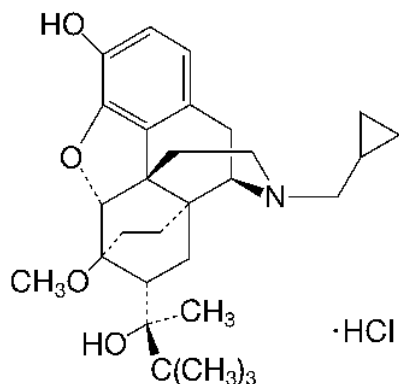
In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

**In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary. The long duration of action of BUNAVAIL should be taken into consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an overdose. Insufficient duration of monitoring may put patients at risk.**

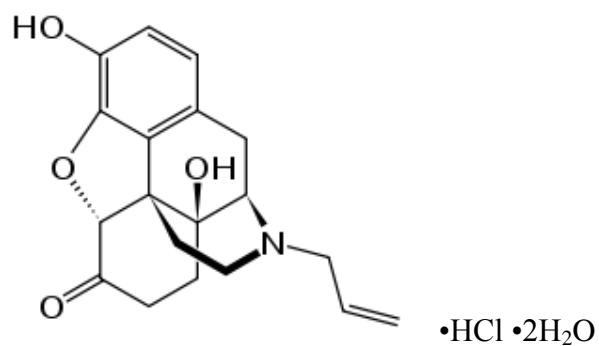
## 11 DESCRIPTION

BUNAVAIL (buprenorphine and naloxone) buccal film is a citrus flavored oral transmucosal form of buprenorphine and naloxone, intended for application to the buccal mucosa. Each dose unit is a yellow rectangular film, with ink marking on the mucoadhesive side. The film adheres upon contact with the moist buccal mucosa. BUNAVAIL contains buprenorphine HCl, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist, and naloxone HCl dihydrate, an opioid receptor antagonist, at a ratio of ~6:1 (ratio of free bases). It is available in three strengths: 2.1 mg buprenorphine with 0.3 mg naloxone in a 2.2 cm<sup>2</sup> film; 4.2 mg buprenorphine with 0.7 mg naloxone in a 4.4 cm<sup>2</sup> film; and 6.3 mg buprenorphine with 1 mg naloxone in a 6.5 cm<sup>2</sup> film. Each film also contains carboxymethylcellulose sodium, citric acid, citrus blend flavor, dibasic sodium phosphate, blue ink, hydroxyethyl cellulose, hydroxypropyl cellulose, methylparaben, monobasic sodium phosphate, polycarbophil, propylene glycol, propylparaben, yellow iron oxide, sodium benzoate, sodium hydroxide, sodium saccharin, vitamin E acetate, and purified water. The blue ink contains FD&C blue #1, ethanol, purified shellac, acetone, ammonium hydroxide and water.

Chemically, buprenorphine HCl, USP is 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- $\alpha$ -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- $\alpha$ -methyl-, hydrochloride, [5 $\alpha$ ,7 $\alpha$ (S)]. It has the following chemical structure:



Buprenorphine HCl has the molecular formula  $C_{29}H_{41}NO_4 \cdot HCl$  and the molecular weight is 504.10. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane. Chemically, naloxone HCl dihydrate, USP is morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5 $\alpha$ )-, dihydrate. It has the following chemical structure:



Naloxone hydrochloride dihydrate has the molecular formula  $C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$  and the molecular weight is 399.87. It is a white to slightly off-white powder, and is freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

BUNAVAIL buccal film contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms, if administered parenterally, in individuals physically dependent on full opioid agonists.

### 12.2 Pharmacodynamics

#### *Subjective Effects:*

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In opioid-experienced subjects who were not physically dependent, acute sublingual doses of buprenorphine/naloxone tablets produced opioid agonist effects which reached a maximum between doses of 8/2 mg and 16/4 mg buprenorphine/naloxone, which corresponds to BUNAVAIL buccal doses of 4.2 mg/0.7 mg and 8.4 mg/1.4 mg buprenorphine/naloxone, respectively.

Opioid agonist ceiling effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

### ***Physiological Effects:***

Buprenorphine in IV (2, 4, 8, 12, and 16 mg) and sublingual (12 mg) doses have been administered in opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O<sub>2</sub> saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O<sub>2</sub> saturation to the same degree.

### ***Effect of Naloxone:***

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and buprenorphine/naloxone tablets were similar at equivalent dose levels of buprenorphine. Naloxone had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine/naloxone, when administered sublingually to an opioid-dependent cohort, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. This finding suggests that the naloxone in buprenorphine/naloxone products may deter injection of buprenorphine/naloxone products by persons with active substantial heroin or other full agonist mu-opioid dependence. However, clinicians should be aware that some opioid-dependent persons, particularly those with a low level of full agonist mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route. In methadone-maintained patients and heroin-dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid

withdrawal signs and symptoms and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal signs and symptoms that were ratio-dependent; the most intense withdrawal signs and symptoms were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio.

## 12.3 Pharmacokinetics

### ***Absorption:***

Plasma levels of buprenorphine and naloxone increased with the buccal dose of BUNAVAIL buccal film. There was wide inter-patient variability in the buccal absorption of buprenorphine and naloxone, but within subjects the variability was low. Both  $C_{max}$  and AUC of buprenorphine increased with the increase in dose (in the range of 0.875 to 6.3 mg), although the increase was not directly dose-proportional. Naloxone did not affect the pharmacokinetics of buprenorphine.

BUNAVAIL has been shown to have different bioavailability compared to SUBOXONE tablet. The exposure of buprenorphine from one BUNAVAIL 4.2 mg/0.7 mg buccal film was equivalent to one SUBOXONE 8 mg/2 mg sublingual tablet. The naloxone exposure from BUNAVAIL buccal film was 33% less than with SUBOXONE sublingual tablets.

The co-administration of liquids reduced the systemic exposure up to 59% for buprenorphine and up to 76% for naloxone from BUNAVAIL, depending on the pH of the liquid, in comparison to the administration of BUNAVAIL when no liquid was co-administered [see *Method of Administration* (2.2)].

### ***Distribution:***

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

Naloxone is approximately 45% protein bound, primarily to albumin.

### ***Metabolism:***

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

### ***Elimination:***

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of

the buprenorphine and norbuprenorphine was free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). Based on all studies performed with BUNAVAIL buccal film, buprenorphine has a mean elimination half-life from plasma ranging from 16.4 to 27.5 hours and naloxone has a mean elimination half-life from plasma ranging from 1.9 to 2.4 hours.

***Drug-drug Interactions:***

*CYP3A4 Inhibitors and Inducers:* Subjects receiving BUNAVAIL buccal film should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors are co-administered and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving BUNAVAIL buccal film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered [see *Drug Interactions (7.1)*].

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in-vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

***Special Population:***

*Hepatic Impairment:* In a pharmacokinetic study, the disposition of buprenorphine and naloxone were determined in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine and naloxone in patients with hepatic impairment were compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean  $C_{max}$ ,  $AUC_{0-last}$ , and half-life values of both buprenorphine and naloxone were not clinically significant. No dosing adjustment is needed in patients with mild hepatic impairment.

For subjects with moderate and severe hepatic impairment, mean  $C_{max}$ ,  $AUC_{0-last}$ , and half-life values of both buprenorphine and naloxone were increased; the effects on naloxone are greater than that on buprenorphine ([Table 3](#)).

**Table 3**

**Changes in Pharmacokinetic Parameters in Subjects With Moderate and Severe Hepatic Impairment**

Hepatic Impairment	PK Parameters	Increase in buprenorphine compared to healthy subjects	Increase in naloxone compared to healthy subjects
Moderate	$C_{max}$	8%	170%

	AUC <sub>0-last</sub>	64%	218%
	Half-life	35%	165%
Severe	C <sub>max</sub>	72%	1030%
	AUC <sub>0-last</sub>	181%	1302%
	Half-life	57%	122%

The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than subjects with moderate hepatic impairment, and therefore the clinical impact of these effects is likely to be greater in patients with severe hepatic impairment than in patients with moderate hepatic impairment. Buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment [see *Warnings and Precautions (5.11)* and *Use in Specific Populations (8.6)*].

*HCV infection:* In subjects with HCV (hepatitis C virus) infection but no sign of hepatic impairment, the changes in the mean C<sub>max</sub>, AUC<sub>0-last</sub>, and half-life values of buprenorphine and naloxone were not clinically significant in comparison to healthy subjects without HCV infection. No dosing adjustment is needed in patients with HCV infection.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**BUNAVAIL buccal film has been shown to have differences in bioavailability compared to buprenorphine/naloxone-containing sublingual products. The exposure margins listed below are based on body surface area comparisons (mg/m<sup>2</sup>) to the recommended human sublingual dose of 16 mg buprenorphine from Suboxone, which is equivalent to a recommended human buccal dose (RHD) of 8.4 mg buprenorphine from Bunavail.**

#### **Carcinogenicity:**

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 RHD 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.

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 carcinogenic at dietary doses up to 100 mg/kg/day (estimated buprenorphine exposure was approximately 30 times the RHD).

### **Mutagenicity:**

The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli*. The combination was not clastogenic in an in vitro cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat.

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* “rec” assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E.coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of [<sup>3</sup>H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

### **Impairment of Fertility:**

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the RHD) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the RHD) had no adverse effect on fertility.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

BUNAVAIL is supplied in individually-sealed foil packages. BUNAVAIL is supplied in three dosage strengths. Each unit is individually wrapped in a child resistant foil package. These foil packages are packed 30 per box.

Each dosage unit is a yellow, rectangular film, with a dosage marking printed on the mucoadhesive side. The dosage strength of each unit is indicated by the dosage marking on the mucoadhesive side of the dose unit, and the dosage strength is marked on the foil package and the 30-unit box. See package and carton for product information.

BUNAVAIL	Dosage Marking	Package Color *	NDC Number
2.1 mg / 0.3 mg buprenorphine / naloxone	BN2	Purple	NDC 59385-012-30
4.2 mg / 0.7 mg buprenorphine / naloxone	BN4	Blue	NDC 59385-014-30
6.3 mg / 1 mg buprenorphine / naloxone	BN6	Orange	NDC 59385-016-30

\* Colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

Store at 20-25°C (68-77°F), with excursions permitted between 15-30°C (59°F-86°F) until ready to use. Protect BUNAVAIL from freezing and moisture. Do not use if the foil package has been damaged.

**Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children.** Destroy any unused medication appropriately [see *Patient Counseling Information (17.2)*].

Rx only

## 17 PATIENT COUNSELING INFORMATION

See FDA approved patient labeling ([Medication Guide](#)).

### 17.1 Safe Use

**Before initiating treatment with BUNAVAIL buccal film, explain the points listed below to caregivers and patients. Instruct patients to read the Medication Guide each time BUNAVAIL is dispensed because new information may be available**

- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking BUNAVAIL buccal films. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician [see *Warnings and Precautions (5.2)*, *Drug Interactions (7.3)*].
- Patients should be advised that BUNAVAIL buccal films contain an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their films in a safe place, and to protect them from theft.
- Patients should be instructed to keep BUNAVAIL buccal films in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to BUNAVAIL buccal films, medical attention should be sought immediately.
- Patients should be advised never to give BUNAVAIL buccal films to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Patients should be advised that selling or giving away this medication is against the law.

- Patients should be cautioned that BUNAVAIL buccal films may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating machinery. Caution should be taken especially during drug induction and dose adjustment and until individuals are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities [see *Warnings and Precautions (5.11)*].
- Patients should be advised not to change the dosage of BUNAVAIL buccal films without consulting their physician.
- Patients should be advised to take BUNAVAIL buccal films once a day.
- Patients should be informed that BUNAVAIL buccal films can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued.
- Patients should be cautioned that, like other opioids, BUNAVAIL may produce orthostatic hypotension in ambulatory individuals.
- Patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their physician on a tapering schedule and should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Patients should inform their physician if any other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used [see *Drug Interactions (7.1, 7.2 and 7.3)*].
- Women of childbearing potential, who become pregnant or are planning to become pregnant, should be advised to consult their physician regarding the possible effects of using BUNAVAIL buccal films during pregnancy [see *Use in Specific Populations (8.1)*].
- Patients should be warned that buprenorphine passes into breast milk. Advise women who are breastfeeding to monitor the infant for drowsiness and difficulty breathing [see *Use in Specific Populations (8.3)*].
- Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with BUNAVAIL buccal films.
- Patients should be advised that if they miss a dose of BUNAVAIL they should take it as soon as they remember. If it is almost time for the next dose, they should skip the missed dose and take the next dose at the regular time.
- Refer to the Medication Guide for additional information regarding the counseling information.

## 17.2 Disposal of Unused

Unused BUNAVAIL buccal films should be disposed of as soon as they are no longer needed. To dispose of the unused BUNAVAIL films:

1. Remove the BUNAVAIL film from its foil package.

2. Drop the BUNAVAIL film into the toilet.
3. Repeat steps 1 and 2 for each BUNAVAIL film. Flush the toilet after all unneeded films have been deposited into the toilet.

Do not flush the BUNAVAIL films in their foil packages, or cartons down the toilet [see *How Supplied/Storage and Handling (16)*].

In the event that additional assistance is needed in disposing of excess unusable films that remain in the home, call the toll-free number (1-800-469-0261) or seek assistance from the local DEA office.

**Manufactured for:**

**BioDelivery Sciences International, Inc., Raleigh, North Carolina 27612 USA**

BBF-002-PI-APR2015

