BUTRANS- buprenorphine patch, extended release
A-S Medication Solutions LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BUTRANS® safely and effectively. See full prescribing information for BUTRANS.

BUTRANS (buprenorphine) Transdermal System for transdermal administration CIII Initial U.S. Approval: 1981

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE
See full prescribing information for complete boxed warning.

- **BUTRANS contains buprenorphine, a Schedule III controlled substance. Monitor for signs of misuse, abuse, and addiction during BUTRANS therapy (5.1, 9).**
- **Fatal respiratory depression may occur, with highest risk at initiation and with dose increases. Instruct patients on proper administration of BUTRANS to reduce the risk (5.2).**
- **Accidental exposure to BUTRANS can result in fatal overdose of buprenorphine, especially in children (5.3).**

RECENT MAJOR CHANGES

Boxed Warning	07/2012
Indications and Usage (1)	07/2012
Dosage and Administration (2)	07/2012
Contraindications (4)	07/2012
Warnings and Precautions (5)	07/2012

INDICATIONS AND USAGE

BUTRANS is a partial opioid agonist product indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. (1)

Limitations of Use

- BUTRANS is not for use:
  - As an as-needed (prn) analgesic (1)
  - For pain that is mild or not expected to persist for an extended period of time (1)
  - For acute pain (1)
  - For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time (1)

DOSAGE AND ADMINISTRATION

- Individualize dosing based on patient's prior analgesic treatment experience, and titrate as needed to provide adequate analgesia and minimize adverse reactions. (2.1, 2.2)
- Instruct patients to wear BUTRANS for 7 days and to wait a minimum of 3 weeks before applying to the same site. (2.1)
- Do not abruptly discontinue BUTRANS in a physically dependent patient. (2.3, 5.17)

DOSAGE FORMS AND STRENGTHS

- **Transdermal system**, 5 mcg/hour, 10 mcg/hour, and 20 mcg/hour. (3)

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus (4)
- Hypersensitivity to buprenorphine (4)

WARNINGS AND PRECAUTIONS

- Elderly, cachectic, and debilitated patients, and patients with chronic pulmonary disease: Monitor closely because of

increased risk of respiratory depression. (5.4, 5.5)

- Interaction with CNS depressants, especially benzodiazepines: Consider dose reduction of one or both drugs because of additive effects. (5.6, 7.2, 7.3)
- Avoid in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications. (5.7, 12.2)
- Hypotensive effects: Monitor during dose initiation and titration. (5.8)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression and avoid use of BUTRANS in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.9)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) include: nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, and application site rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- CYP3A4 inducers: May increase clearance of buprenorphine. (7.1)
- Interaction with CNS depressants: Consider dose reduction of one or both drugs because of additive effects. (5.6, 7.3)
- Muscle relaxants may enhance the action of BUTRANS and produce an increased degree of respiratory depression. (7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: BUTRANS is not recommended for use during pregnancy. (8.1)
- Nursing Mothers: Buprenorphine has been detected in human milk. Closely monitor infants of nursing women receiving BUTRANS. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

BUTRANS contains buprenorphine, an opioid agonist and Schedule III controlled substance with an abuse liability similar to other Schedule III opioids, legal or illicit *[see Warnings and Precautions (5.1)]*. Assess each patient's risk for opioid abuse or addiction prior to prescribing BUTRANS. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving BUTRANS for signs of misuse, abuse, and addiction during treatment *[see Drug Abuse and Dependence (9)]*.

Life-Threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of BUTRANS, even when the drug has been used as recommended and not misused or abused *[see Warnings and Precautions (5.2)]*. Proper dosing and titration are essential and BUTRANS should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of BUTRANS or following a dose increase.

Accidental Exposure

Accidental exposure to BUTRANS, especially in children, can result in a fatal overdose of buprenorphine *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

BUTRANS is indicated for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Use

BUTRANS is not for use:

- As an as-needed (prn) analgesic
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with BUTRANS *[see Warnings and Precautions (5.2)]*. Overestimating the BUTRANS dose when converting patients from another opioid medication can result in fatal overdose with the first dose *[see Overdosage (10)]*.

Consider the following factors when selecting an initial dose of BUTRANS:

- Total daily dose, potency, and any prior opioid the patient has been taking previously;
- Reliability of the relative potency estimate used to calculate the equivalent dose of buprenorphine needed (Note: potency estimates may vary with the route of administration);

- Patient's degree of opioid experience and opioid tolerance;
- General condition and medical status of the patient;
- Concurrent medication;
- Type and severity of the patient's pain.

BUTRANS is for transdermal use (on intact skin) only. Each BUTRANS is intended to be worn for 7 days.

Instruct patients not to use BUTRANS if the pouch seal is broken or the patch is cut, damaged, or changed in any way and not to cut BUTRANS.

BUTRANS as the First Opioid Analgesic
Initiate treatment with BUTRANS 5 mcg/hour.

Conversion from Other Opioids to BUTRANS
There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids.

Prior Total Daily Dose of Opioid Less than 30 mg of Oral Morphine Equivalents per Day:
Initiate treatment with BUTRANS 5 mcg/hour.

Prior Total Daily Dose of Opioid Between 30 mg to 80 mg of Oral Morphine Equivalents per Day:
Taper the patient's current around-the-clock opioids for up to 7 days to no more than 30 mg of morphine or equivalent per day before beginning treatment with BUTRANS. Then initiate treatment with BUTRANS 10 mcg/hour. Patients may use short-acting analgesics as needed until analgesic efficacy with BUTRANS is attained.

Prior Total Daily Dose of Opioid Greater than 80 mg of Oral Morphine Equivalents per Day:
BUTRANS 20 mcg/hour may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents. Consider the use of an alternate analgesic.

Table 1: Initial BUTRANS Dose

Current Opioid Analgesic	**Current Daily Dose**	
Oral Morphine Equivalent	<30 mg	30-80 mg
	⇩	⇩
Recommended BUTRANS Starting Dose	**5 mcg/hour**	**10 mcg/hour**

2.2 Titration and Maintenance of Therapy

Individually titrate BUTRANS to a dose that provides adequate analgesia and minimizes adverse reactions. The minimum BUTRANS titration interval is 72 hours, based on the pharmacokinetic profile and time to reach steady state levels *[see Clinical Pharmacology (12.3)]*.

The maximum BUTRANS dose is 20 mcg/hour. **Do not exceed a dose of one 20 mcg/hour BUTRANS system due to the risk of QTc interval prolongation.** In a clinical trial, BUTRANS 40 mcg/hour (given as two BUTRANS 20 mcg/hour systems) resulted in prolongation of the QTc interval *[see Warnings and Precautions (5.7), and Clinical Pharmacology (12.2)]*.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the BUTRANS dose to decrease the level of pain. Because steady-state plasma concentrations are approximated within 72 hours, BUTRANS dosage adjustments may be done every 3 days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid or non-opioid medication.

If signs of excessive opioid-related adverse reactions are observed, the current patch may be removed or next dose may be reduced. Adjust the dose to obtain an appropriate balance between the management

of pain and opioid-related adverse reactions.

2.3 Cessation of Therapy

When the patient no longer requires therapy with BUTRANS, use a gradual downward titration of the dose every 7 days to prevent signs and symptoms of withdrawal in the physically dependent patient; consider introduction of an appropriate immediate-release opioid medication. Do not abruptly discontinue BUTRANS.

2.4 Patients with Hepatic Impairment

BUTRANS has not been evaluated in patients with severe hepatic impairment. As BUTRANS is only intended for 7-day application, consider use of an alternate analgesic that may permit more flexibility with the dosing in patients with severe hepatic impairment *[see Warnings and Precautions (5.10), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

2.5 Administration of BUTRANS

Instruct patients to apply immediately after removal from the individually sealed pouch. Instruct patients not to use BUTRANS if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

Apply BUTRANS to the upper outer arm, upper chest, upper back or the side of the chest. These 4 sites (each present on both sides of the body) provide 8 possible application sites. Rotate BUTRANS among the 8 described skin sites. After BUTRANS removal, wait a minimum of 21 days before reapplying to the same skin site *[see Clinical Pharmacology (12.3)]*.

Apply BUTRANS to a hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped, not shaven. Do not apply BUTRANS to irritated skin. If the application site must be cleaned, clean the site with water only. Do not use soaps, alcohol, oils, lotions, or abrasive devices. Allow the skin to dry before applying BUTRANS.

If problems with adhesion of BUTRANS occur, the edges may be taped with first aid tape.

If BUTRANS falls off during the 7 days dosing interval, dispose of the transdermal system properly and place a new BUTRANS on at a different skin site.

When changing the system, instruct patients to remove BUTRANS, fold it over on itself, and flush it down the toilet. Alternatively, BUTRANS can be sealed in the Patch-Disposal Unit provided and then disposed of in the trash. <u>Never throw BUTRANS away in the trash without sealing it in the Patch-Disposal Unit.</u>

See the Instructions for Use for step-by-step instructions for applying BUTRANS.

If the buprenorphine-containing adhesive matrix accidentally contacts the skin, instruct patients or caregivers to wash the area with water and not to use soap, alcohol, or other solvents to remove the adhesive because they may enhance the absorption of the drug.

3 DOSAGE FORMS AND STRENGTHS

BUTRANS is a rectangular or square, beige-colored system consisting of a protective liner and functional layers. BUTRANS is available in three strengths:

- BUTRANS 5 mcg/hour Transdermal System (dimensions: 45 mm by 45 mm)
- BUTRANS 10 mcg/hour Transdermal System (dimensions: 45 mm by 68 mm)
- BUTRANS 20 mcg/hour Transdermal System (dimensions: 72 mm by 72 mm)

4 CONTRAINDICATIONS

BUTRANS is contraindicated in patients with:

- Significant respiratory depression

- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity (e.g., anaphylaxis) to buprenorphine *[see Warnings and Precautions (5.12), and Adverse Reactions (6)]*

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

BUTRANS contains buprenorphine, a partial agonist at the mu opioid receptor and a Schedule III controlled substance. Buprenorphine can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing BUTRANS in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient's risk for opioid abuse or addiction prior to prescribing BUTRANS. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of BUTRANS by chewing, swallowing, snorting or injecting buprenorphine extracted from the transdermal system will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death *[see Overdosage (10)]*.

Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Respiratory depression is the primary risk of BUTRANS. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of BUTRANS, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with BUTRANS and following dose increases. Instruct patients against use by individuals other than the patient for whom BUTRANS was prescribed and to keep BUTRANS out of the reach of children, as such inappropriate use may result in fatal respiratory depression.

To reduce the risk of respiratory depression, proper dosing and titration of BUTRANS are essential *[see Dosage and Administration (2.1, 2.2)]*. Overestimating the BUTRANS dose when converting patients from another opioid product can result in fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-release opioids when used as recommended and not misused or abused.

To further reduce the risk of respiratory depression, consider the following:

- Proper dosing and titration are essential and BUTRANS should only be prescribed by healthcare

professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.
- BUTRANS is contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression *[see Contraindications (4)]*.

5.3 Accidental Exposure

Accidental exposure to BUTRANS, especially in children, can result in a fatal overdose of buprenorphine.

5.4 Elderly, Cachectic, and Debilitated Patients

Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance compared to younger, healthier patients. Therefore, monitor such patients closely, particularly when initiating and titrating BUTRANS and when BUTRANS is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*.

5.5 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with BUTRANS, as in these patients, even usual therapeutic doses of BUTRANS may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.6 Interactions with Alcohol, CNS Depressants, and Illicit Drugs

Hypotension, profound sedation, coma or respiratory depression may result if BUTRANS is added to a regimen that includes other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, muscle relaxants, other opioids). When considering the use of BUTRANS in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient’s response, including the degree of tolerance that has developed to CNS depression. Additionally, consider the patient’s use, if any, of alcohol or illicit drugs that cause CNS depression. If BUTRANS therapy is to be initiated in a patient taking a CNS depressant, start with a lower BUTRANS dose than usual and monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.3)]*.

5.7 QTc Prolongation

A positive-controlled study of the effects of BUTRANS on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a BUTRANS dose of 10 mcg/hour; however, a BUTRANS dose of 40 mcg/hour (given as two BUTRANS 20 mcg/hour Transdermal Systems) was observed to prolong the QTc interval *[see Clinical Pharmacology (12.2)]*.

Consider these observations in clinical decisions when prescribing BUTRANS to patients with hypokalemia or clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Avoid the use of BUTRANS in patients with a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide).

5.8 Hypotensive Effects

BUTRANS may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs

(e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7.3)]*. Monitor these patients for signs of hypotension after initiating or titrating the dose of BUTRANS.

5.9 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking BUTRANS who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with BUTRANS. BUTRANS may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of BUTRANS in patients with impaired consciousness or coma.

5.10 Hepatotoxicity

Although not observed in BUTRANS chronic pain clinical trials, cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving sublingual buprenorphine for the treatment of opioid dependence, both in clinical trials and in post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of 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 injection drug abuse may have played a causative or contributory role. For patients at increased risk of hepatotoxicity (e.g., patients with a history of excessive alcohol intake, intravenous drug abuse or liver disease), obtain baseline liver enzyme levels and monitor periodically and during treatment with BUTRANS.

5.11 Application Site Skin Reactions

In rare cases, severe application site skin reactions with signs of marked inflammation including “burn,” “discharge,” and “vesicles” have occurred. Time of onset varies, ranging from days to months following the initiation of BUTRANS treatment. Instruct patients to promptly report the development of severe application site reactions and discontinue therapy.

5.12 Anaphylactic/Allergic Reactions

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

5.13 Application of External Heat

Advise patients and their caregivers to avoid exposing the BUTRANS application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds while wearing the system because an increase in absorption of buprenorphine may occur *[see Clinical Pharmacology (12.3)]*. Advise patients against exposure of the BUTRANS application site and surrounding area to hot water or prolonged exposure to direct sunlight. There is a potential for temperature-dependent increases in buprenorphine released from the system resulting in possible overdose and death.

5.14 Patients with Fever

Monitor patients wearing BUTRANS systems who develop fever or increased core body temperature due to strenuous exertion for opioid side effects and adjust the BUTRANS dose if signs of respiratory or central nervous system depression occur.

5.15 Use in Patients with Gastrointestinal Conditions

BUTRANS is contraindicated in patients with paralytic ileus. Avoid the use of BUTRANS in patients with other GI obstruction.

The buprenorphine in BUTRANS may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms. Opioids may cause increases in the serum amylase.

5.16 Use in Patients with Convulsive or Seizure Disorders

The buprenorphine in BUTRANS may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during BUTRANS therapy.

5.17 Avoidance of Withdrawal

Symptoms of withdrawal include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Significant fluid losses from vomiting and diarrhea can require intravenous fluid administration.

When discontinuing BUTRANS, gradually taper the dose *[see Dosage and Administration (2.3)]*. Do not abruptly discontinue BUTRANS.

5.18 Driving and Operating Machinery

BUTRANS may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of BUTRANS and know how they will react to the medication.

5.19 Use in Addiction Treatment

BUTRANS has not been studied and is not approved for use in the management of addictive disorders.

6 ADVERSE REACTIONS

The following adverse reactions described elsewhere in the labeling include:

- Respiratory Depression *[see Warnings and Precautions (5.2)]*
- QTc Prolongation *[see Warnings and Precautions (5.7)]*
- Hypotensive Effects *[see Warnings and Precautions (5.8)]*
- Application Site Skin Reactions *[see Warnings and Precautions (5.11)]*
- Anaphylactic/Allergic Reactions *[see Warnings and Precautions (5.12)]*
- Gastrointestinal Effects *[see Warnings and Precautions (5.15)]*
- Seizures*[see Warnings and Precautions (5.16)]*

6.1 Clinical Trial Experience

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.

A total of 5,415 patients were treated with BUTRANS in controlled and open-label chronic pain clinical trials. Nine hundred twenty-four subjects were treated for approximately six months and 183 subjects were treated for approximately one year. The clinical trial population consisted of patients with persistent moderate to severe pain.

The most common serious adverse drug reactions (all <0.1%) occurring during clinical trials with BUTRANS were: chest pain, abdominal pain, vomiting, dehydration, and hypertension/blood pressure increased.

The most common adverse events (≥ 2%) leading to discontinuation were: nausea, dizziness, vomiting, headache, and somnolence.

The most common adverse reactions (≥ 5%) reported by patients in clinical trials comparing BUTRANS 10 or 20 mcg/hour to placebo are shown in Table 2, and comparing BUTRANS 20 mcg/hour to BUTRANS 5 mcg/hour are shown in Table 3 below:

Table 2: Adverse Reactions Reported in ≥ 5% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period: Opioid-Naïve Patients

	Open-Label Titration Period	Double-Blind Treatment Period	
	BUTRANS	BUTRANS	Placebo
MedDRA Preferred Term	**(N = 1024)**	**(N = 256)**	**(N = 283)**
Nausea	23%	13%	10%
Dizziness	10%	4%	1%
Headache	9%	5%	5%
Application site pruritus	8%	4%	7%
Somnolence	8%	2%	2%
Vomiting	7%	4%	1%
Constipation	6%	4%	1%

Table 3: Adverse Reactions Reported in ≥ 5% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period: Opioid-Experienced Patients

	Open-Label Titration Period	Double-Blind Treatment Period	
	BUTRANS	BUTRANS 20	BUTRANS 5
MedDRA Preferred Term	**(N = 1160)**	**(N = 219)**	**(N = 221)**
Nausea	14%	11%	6%
Application site pruritus	9%	13%	5%
Headache	9%	8%	3%
Somnolence	6%	4%	2%
Dizziness	5%	4%	2%
Constipation	4%	6%	3%
Application site erythema	3%	10%	5%
Application site rash	3%	8%	6%
Application site irritation	2%	6%	2%

The following table lists adverse reactions that were reported in at least 2.0% of patients in four placebo/active-controlled titration-to-effect trials.

Table 4: Adverse Reactions Reported in Titration-to-Effect Placebo/Active-Controlled Clinical Trials with Incidence ≥ 2%

MedDRA Preferred Term	**BUTRANS (N = 392)**	**Placebo (N = 261)**
Nausea	21%	6%
Application site pruritus	15%	12%
Dizziness	15%	7%
Headache	14%	9%

Somnolence	13%	4%
Constipation	13%	5%
Vomiting	9%	1%
Application site erythema	7%	2%
Application site rash	6%	6%
Dry mouth	6%	2%
Fatigue	5%	1%
Hyperhidrosis	4%	1%
Peripheral edema	3%	1%
Pruritus	3%	0%
Stomach discomfort	2%	0%

The adverse reactions seen in controlled and open-label studies are presented below in the following manner: most common (≥ 5%), common (≥ 1% to < 5%), and less common (< 1%).

The most common adverse reactions (≥ 5%) reported by patients treated with BUTRANS in the clinical trials were nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, and application site rash.

The common (≥ 1% to < 5%) adverse reactions reported by patients treated with BUTRANS in the clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class were:

Gastrointestinal disorders: diarrhea, dyspepsia, and upper abdominal pain

General disorders and administration site conditions: fatigue, peripheral edema, application site irritation, pain, pyrexia, chest pain, and asthenia

Infections and infestations: urinary tract infection, upper respiratory tract infection, nasopharyngitis, influenza, sinusitis, and bronchitis

Injury, poisoning and procedural complications: fall

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: back pain, arthralgia, pain in extremity, muscle spasms, musculoskeletal pain, joint swelling, neck pain, and myalgia

Nervous system disorders: hypoesthesia, tremor, migraine, and paresthesia

Psychiatric disorders: insomnia, anxiety, and depression

Respiratory, thoracic and mediastinal disorders: dyspnea, pharyngolaryngeal pain, and cough

Skin and subcutaneous tissue disorders: pruritus, hyperhidrosis, rash, and generalized pruritus

Vascular disorders: hypertension

Other less common adverse reactions, including those known to occur with opioid treatment, that were seen in < 1% of the patients in the BUTRANS trials include the following in alphabetical order:

Abdominal distention, abdominal pain, accidental injury, affect lability, agitation, alanine aminotransferase increased, angina pectoris, angioedema, apathy, application site dermatitis, asthma aggravated, bradycardia, chills, confusional state, contact dermatitis, coordination abnormal, dehydration, depersonalization, depressed level of consciousness, depressed mood, disorientation, disturbance in attention, diverticulitis, drug hypersensitivity, drug withdrawal syndrome, dry eye, dry skin, dysarthria, dysgeusia, dysphagia, euphoric mood, face edema, flatulence, flushing, gait disturbance, hallucination, hiccups, hot flush, hyperventilation, hypotension, hypoventilation, ileus, insomnia, libido decreased, loss of consciousness, malaise, memory impairment, mental impairment,

mental status changes, miosis, muscle weakness, nervousness, nightmare, orthostatic hypotension, palpitations, psychotic disorder, respiration abnormal, respiratory depression, respiratory distress, respiratory failure, restlessness, rhinitis, sedation, sexual dysfunction, syncope, tachycardia, tinnitus, urinary hesitation, urinary incontinence, urinary retention, urticaria, vasodilatation, vertigo, vision blurred, visual disturbance, weight decreased, and wheezing.

7 DRUG INTERACTIONS

7.1 Hepatic Enzyme Inhibitors and Inducers

CYP3A4 Inhibitors
Co-administration of ketoconazole, a strong CYP3A4 inhibitor, with BUTRANS, did not have any effect on C_{max} (maximum concentration) and AUC (area under the curve) of buprenorphine. Based on this observation, the pharmacokinetics of BUTRANS are not expected to be affected by co-administration of CYP3A4 inhibitors.

However, certain protease inhibitors (PIs) with CYP3A4 inhibitory activity such as atazanavir and atazanavir/ritonavir resulted in elevated levels of buprenorphine and norbuprenorphine following sublingual administration of buprenorphine and naloxone. Patients in this study reported increased sedation, and symptoms of opiate excess have been found in post-marketing reports of patients receiving sublingual buprenorphine and atazanavir with and without ritonavir concomitantly. Atazanavir is both a CYP3A4 and UGT1A1 inhibitor. As such, the drug-drug interaction potential for buprenorphine with CYP3A4 inhibitors is likely to be dependent on the route of administration as well as the specificity of enzyme inhibition *[see Clinical Pharmacology (12.3)]*.

CYP3A4 Inducers
The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied. Monitor patients receiving concurrent therapy with BUTRANS and CYP3A4 inducers (e.g., phenobarbital, carbamazepine, phenytoin, rifampin) closely for reduced efficacy or signs of withdrawal *[see Clinical Pharmacology (12.3)]*.

7.2 Benzodiazepines

There have been a number of reports regarding coma and death associated with the misuse and abuse of the combination of buprenorphine and benzodiazepines. In many, but not all of these cases, buprenorphine was misused by self-injection of crushed buprenorphine tablets. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. Closely monitor patients with concurrent use of BUTRANS and benzodiazepines. Warn patients that it is extremely dangerous to self-administer benzodiazepines while taking BUTRANS, and warn patients to use benzodiazepines concurrently with BUTRANS only as directed by their physician.

7.3 CNS Depressants

Concurrent use of BUTRANS and other central nervous system (CNS) depressants (e.g., sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, and profound sedation or coma. Monitor patients receiving CNS depressants and BUTRANS for signs of respiratory depression and hypotension. When such combined therapy is contemplated, reduce the initial dose of one or both agents.

7.4 Skeletal Muscle Relaxants

BUTRANS, like other opioids, may interact with skeletal muscle relaxants to enhance neuromuscular blocking action and increase respiratory depression.

7.5 Anticholinergics

Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when BUTRANS is used concurrently with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects (Pregnancy Category C)
There are no adequate and well-controlled studies with BUTRANS in pregnant women. BUTRANS should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the fetus. In animal studies, buprenorphine caused an increase in the number of stillborn offspring, reduced litter size, and reduced offspring growth in rats at maternal exposure levels that were approximately 10 times that of human subjects who received one BUTRANS 20 mcg/hour, the maximum recommended human dose (MRHD).

Studies in rats and rabbits demonstrated no evidence of teratogenicity following BUTRANS or subcutaneous (SC) administration of buprenorphine during the period of major organogenesis. Rats were administered up to one BUTRANS 20 mcg/hour every 3 days (gestation days 6, 9, 12, & 15) or received daily SC buprenorphine up to 5 mg/kg (gestation days 6-17). Rabbits were administered four BUTRANS 20 mcg/hour every 3 days (gestation days 6, 9, 12, 15, 18, & 19) or received daily SC buprenorphine up to 5 mg/kg (gestation days 6-19). No teratogenicity was observed at any dose. AUC values for buprenorphine with BUTRANS application and SC injection were approximately 110 and 140 times, respectively, that of human subjects who received the MRHD of one BUTRANS 20 mcg/hour.

Non-Teratogenic Effects
In a peri- and post-natal study conducted in pregnant and lactating rats, administration of buprenorphine either as BUTRANS or SC buprenorphine was associated with toxicity to offspring. Buprenorphine was present in maternal milk. Pregnant rats were administered 1/4 of one BUTRANS 5 mcg/hour every 3 days or received daily SC buprenorphine at doses of 0.05, 0.5, or 5 mg/kg from gestation day 6 to lactation day 21 (weaning). Administration of BUTRANS or SC buprenorphine at 0.5 or 5 mg/kg caused maternal toxicity and an increase in the number of stillborns, reduced litter size, and reduced offspring growth at maternal exposure levels that were approximately 10 times that of human subjects who received the MRHD of one BUTRANS 20 mcg/hour. Maternal toxicity was also observed at the no observed adverse effect level (NOAEL) for offspring.

8.2 Labor and Delivery

BUTRANS is not for use in women immediately prior to and during labor, where use of short-acting analgesics or other analgesic techniques are more appropriate *[see Indications and Usage (1)]*. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. An opioid antagonist, such as naloxone, should be available for reversal of opioid-induced respiratory depression in the neonate in such situations.

8.3 Nursing Mothers

Buprenorphine is excreted in breast milk. The amount of buprenorphine received by the infant varies

depending on the maternal plasma concentration, the amount of milk ingested by the infant, and the extent of first pass metabolism.

Withdrawal symptoms can occur in breast-feeding infants when maternal administration of buprenorphine is stopped.

Because of the potential for adverse reactions in nursing infants from BUTRANS, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of BUTRANS in patients under 18 years of age has not been established.

8.5 Geriatric Use

Of the total number of subjects in the clinical trials (5,415), BUTRANS was administered to 1,377 patients aged 65 years and older. Of those, 457 patients were 75 years of age and older. In the clinical program, the incidences of selected BUTRANS-related AEs were higher in older subjects. The incidences of application site AEs were slightly higher among subjects < 65 years of age than those ≥ 65 years of age for both BUTRANS and placebo treatment groups.

In a single-dose study of healthy elderly and healthy young subjects treated with BUTRANS 10 mcg/hour, the pharmacokinetics were similar. In a separate dose-escalation safety study, the pharmacokinetics in the healthy elderly and hypertensive elderly subjects taking thiazide diuretics were similar to those in the healthy young adults. In the elderly groups evaluated, adverse event rates were similar to or lower than rates in healthy young adult subjects, except for constipation and urinary retention, which were more common in the elderly. Although specific dose adjustments on the basis of advanced age are not required for pharmacokinetic reasons, use caution in the elderly population to ensure safe use *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

In a study utilizing intravenous buprenorphine, peak plasma levels (C_{max}) and exposure (AUC) of buprenorphine in patients with mild and moderate hepatic impairment did not increase as compared to those observed in subjects with normal hepatic function. BUTRANS has not been evaluated in patients with severe hepatic impairment. As BUTRANS is intended for 7-day dosing, consider the use of alternate analgesic therapy in patients with severe hepatic impairment *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3)]*.

8.7 Neonatal Opioid Withdrawal Syndrome

Chronic maternal use of buprenorphine during pregnancy can affect the fetus with subsequent withdrawal signs. Neonatal withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration and severity of neonatal withdrawal syndrome vary based on the drug used, duration of use, the dose of last maternal use, and rate of elimination drug by the newborn. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

BUTRANS contains buprenorphine, a mu opioid partial agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. BUTRANS can be abused and is subject to misuse, abuse, addiction and criminal diversion.

9.2 Abuse

Abuse of BUTRANS poses a hazard of overdose and death. This risk is increased with compromise of the BUTRANS Transdermal System and with concurrent abuse of alcohol or other substances. BUTRANS has been diverted for non-medical use.

All patients treated with opioids, including BUTRANS, require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

BUTRANS may be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state law, is strongly advised.

The risks of misuse and abuse should be considered when prescribing or dispensing BUTRANS. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.

Risks Specific to the Abuse of BUTRANS
BUTRANS is intended for transdermal use only. Abuse of BUTRANS poses a risk of overdose and death. This risk is increased with concurrent abuse of BUTRANS with alcohol and other substances including other opioids and benzodiazepines *[see Warnings and Precautions (5.6), and Drug Interactions (7.2)]*. Compromising the transdermal delivery system will result in the uncontrolled delivery of buprenorphine and pose a significant risk to the abuser that could result in overdose and death *[see Warnings and Precautions (5.1)]*. Abuse may occur by applying the transdermal system in the absence of legitimate purpose, or by swallowing, snorting or injecting buprenorphine extracted from the transdermal system.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of

disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

BUTRANS should not be abruptly discontinued *[see Dosage and Administration (2.3)]*. If BUTRANS is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.7)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with BUTRANS is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. High doses of naloxone, 10-35 mg/70 kg, may be of limited value in the management of buprenorphine overdose. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride (a respiratory stimulant) has also been used.

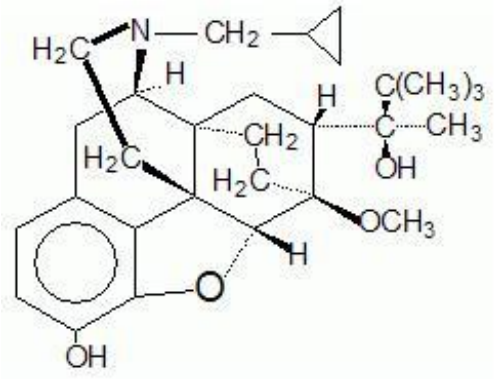
Remove BUTRANS immediately. Because the duration of reversal would be expected to be less than the duration of action of buprenorphine from BUTRANS, carefully monitor the patient until spontaneous respiration is reliably re-established. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects as buprenorphine continues to be absorbed from the skin. After removal of BUTRANS, the mean buprenorphine concentrations decrease approximately 50% in 12 hours (range 10-24 hours) with an apparent terminal half-life of approximately 26 hours. Due to this long apparent terminal half-life, patients may require monitoring and treatment for at least 24 hours.

In an individual physically dependent on opioids, administration of an opioid receptor antagonist may precipitate an acute withdrawal. The severity of the withdrawal produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient with an opioid antagonist, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

BUTRANS is a transdermal system providing systemic delivery of buprenorphine, a mu opioid partial agonist analgesic, continuously for 7 days. The chemical name of buprenorphine is 6,14-

ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- -(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy- -methyl-, [5 , 7 , (S)]. The structural formula is:



The molecular weight of buprenorphine is 467.6; the empirical formula is $C_{29}H_{41}NO_4$. Buprenorphine occurs as a white or almost white powder and is very slightly soluble in water, freely soluble in acetone, soluble in methanol and ether, and slightly soluble in cyclohexane. The pKa is 8.5 and the melting point is about 217°C.

System Components and Structure

Three different strengths of BUTRANS are available: 5, 10, and 20 mcg/hour (Table 5). The proportion of buprenorphine mixed in the adhesive matrix is the same in each of the 3 strengths. The amount of buprenorphine released from each system per hour is proportional to the active surface area of the system. The skin is the limiting barrier to diffusion from the system into the bloodstream.

Table 5: BUTRANS Product Specifications

Buprenorphine Delivery Rate (mcg/hour)	Active Surface Area (cm^2)	Total Buprenorphine Content (mg)
BUTRANS 5	6.25	5
BUTRANS 10	12.5	10
BUTRANS 20	25	20

BUTRANS is a rectangular or square, beige-colored system consisting of a protective liner and functional layers. Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a beige-colored web backing layer; (2) an adhesive rim without buprenorphine; (3) a separating layer over the buprenorphine-containing adhesive matrix; (4) the buprenorphine-containing adhesive matrix; and (5) a peel-off release liner. Before use, the release liner covering the adhesive layer is removed and discarded.

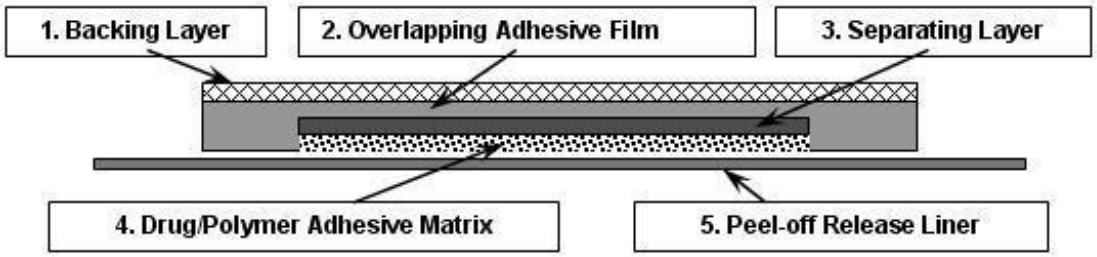


Figure 1: Cross-Section Diagram of BUTRANS (not to scale).

The active ingredient in BUTRANS is buprenorphine. The inactive ingredients in each system are: levulinic acid, oleyl oleate, povidone, and polyacrylate cross-linked with aluminum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Buprenorphine is a partial agonist at mu opioid receptors. Buprenorphine is also an antagonist at kappa opioid receptors, an agonist at delta opioid receptors, and a partial agonist at ORL-1 (nociceptin) receptors. Its clinical actions result from binding to the opioid receptors.

12.2 Pharmacodynamics

Effects on the Central Nervous System
The principal actions of therapeutic value of buprenorphine are analgesia and sedation. Specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects.

Buprenorphine produces respiratory depression by direct action on brainstem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brainstem respiratory centers to increases in carbon dioxide tension, and to electrical stimulation.

Buprenorphine causes miosis, even in total darkness, and little tolerance develops to this effect. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia in the setting of buprenorphine overdose.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
Gastric, biliary, and pancreatic secretions are decreased by buprenorphine. Buprenorphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Buprenorphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Effects on the Cardiovascular System
Buprenorphine may cause a reduction in blood pressure.

Effects on Cardiac Electrophysiology
The effect of BUTRANS 10 mcg/hour and 2 x BUTRANS 20 mcg/hour on QTc interval was evaluated in a double-blind (BUTRANS vs. placebo), randomized, placebo and active-controlled (moxifloxacin 400 mg, open label), parallel-group, dose-escalating, single-dose study in 132 healthy male and female subjects aged 18 to 55 years. The dose escalation sequence for BUTRANS during the titration period was: BUTRANS 5 mcg/hour for 3 days, then BUTRANS 10 mcg/hour for 3 days, then BUTRANS 20 mcg/hour for 3 days, then 2 x BUTRANS 20 mcg/hour for 4 days. The QTc evaluation was performed during the third day of BUTRANS 10 mcg/hour and the fourth day of 2 x BUTRANS 20 mcg/hour when the plasma levels of buprenorphine were at steady state for the corresponding doses *[see Warnings and Precautions (5.7)]*.

There was no clinically meaningful effect on mean QTc with a BUTRANS dose of 10 mcg/hour. A BUTRANS dose of 40 mcg/hour (given as two 20 mcg/hour BUTRANS Transdermal Systems) prolonged mean QTc by a maximum of 9.2 (90% CI: 5.2-13.3) msec across the 13 assessment time points.

Effects on the Endocrine System
Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

12.3 Pharmacokinetics

Absorption
Each BUTRANS system provides delivery of buprenorphine for 7 days. Steady state was achieved during the first application by Day 3 (see Figure 2).

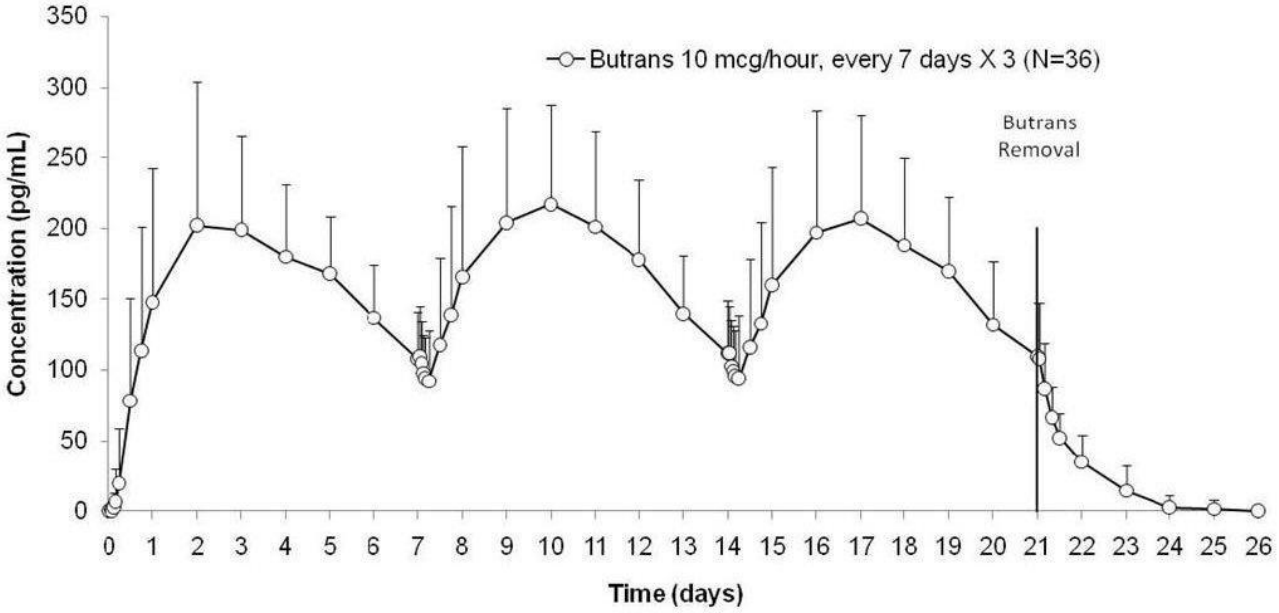


Figure 2 Mean (SD) Buprenorphine Plasma Concentrations Following Three Consecutive Applications of BUTRANS 10 mcg/hour (N = 36 Healthy Subjects)

BUTRANS 5, 10, and 20 mcg/hour provide dose-proportional total buprenorphine exposures (AUC) following 7-day applications. BUTRANS single 7-day application and steady-state pharmacokinetic parameters are summarized in Table 6. Plasma buprenorphine concentrations after titration showed no further change over the 60-day period studied. After removal of BUTRANS, mean buprenorphine concentrations decrease approximately 50% within 10 - 24 hours, followed by decline with an apparent terminal half-life of approximately 26 hours.

Table 6: Pharmacokinetic Parameters of BUTRANS in Healthy Subjects, Mean (%CV)

Single 7-day Application	**AUC_{inf} (pg.h/mL)**	**C_{max} (pg/mL)**
BUTRANS 5 mcg/hour	12087 (37)	176 (67)
BUTRANS 10 mcg/hour	27035 (29)	191 (34)
BUTRANS 20 mcg/hour	54294 (36)	471 (49)
Multiple 7-day Applications	**$AUC_{tau,ss}$ (pg.h/mL)**	**$C_{max,ss}$ (pg/mL)**
BUTRANS 10 mcg/hour, steady-state	27543 (33)	224 (35)

Transdermal delivery studies showed that intact human skin is permeable to buprenorphine. In clinical pharmacology studies, the median time for BUTRANS 10 mcg/hour to deliver quantifiable buprenorphine concentrations (≥ 25 pg/mL) was approximately 17 hours. The absolute bioavailability of BUTRANS relative to IV administration, following a 7-day application, is approximately 15% for all doses (BUTRANS 5, 10, and 20 mcg/hour).

Distribution

Buprenorphine is approximately 96% bound to plasma proteins, mainly to alpha- and beta-globulin.

Studies of IV buprenorphine have shown a large volume of distribution (approximately 430 L), implying extensive distribution of buprenorphine.

Following IV administration, buprenorphine and its metabolites are secreted into bile and excreted in urine. CSF buprenorphine concentrations appear to be approximately 15-25% of concurrent plasma concentrations.

Metabolism

Buprenorphine metabolism in the skin following BUTRANS application is negligible. Following transdermal application, buprenorphine is eliminated via hepatic metabolism, with subsequent biliary excretion and renal excretion of soluble metabolites.

Buprenorphine primarily undergoes *N*-dealkylation by CYP3A4 to norbuprenorphine and glucuronidation by UGT-isoenzymes (mainly UGT1A1 and 2B7) to buprenorphine 3β-*O*-glucuronide. Norbuprenorphine, the major metabolite, is also glucuronidated (mainly UGT1A3) prior to excretion.

Norbuprenorphine is the only known active metabolite of buprenorphine. It has been shown to be a respiratory depressant in rats, but only at concentrations at least 50-fold greater than those observed following application to humans of BUTRANS 20 mcg/hour.

Since metabolism and excretion of buprenorphine occur mainly via hepatic elimination, reductions in hepatic blood flow induced by some general anesthetics (e.g., halothane) and other drugs may result in a decreased rate of hepatic elimination of the drug, resulting in increased plasma concentrations.

Excretion

Following intramuscular administration of 2 mcg/kg dose of buprenorphine, approximately 70% of the dose was excreted in feces within 7 days. Approximately 27% was excreted in urine. The total clearance of buprenorphine is approximately 55 L/hour in postoperative patients.

Drug Interactions

Effect of CYP3A4 inhibitors

In a drug-drug interaction study, BUTRANS 10 mcg/hour (single dose x 7 days) was co-administered with 200 mg ketoconazole, a strong CYP3A4 inhibitor or ketoconazole placebo twice daily for 11 days and the pharmacokinetics of buprenorphine and its metabolites were evaluated. Plasma buprenorphine concentrations did not accumulate during co-medication with ketoconazole 200 mg twice daily. Based on the results from this study, metabolism during therapy with BUTRANS is not expected to be affected by co-administration of CYP3A4 inhibitors *[see Drug Interactions (7.1)]*.

Antiretroviral agents have been evaluated for CYP3A4 mediated interactions with sublingual buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) do not appear to have clinically significant interactions with buprenorphine. However, certain protease inhibitors (PIs) with CYP3A4 inhibitory activity such as atazanavir and atazanavir/ritonavir resulted in elevated levels of buprenorphine and norbuprenorphine when buprenorphine and naloxone were administered sublingually. C_{max} and AUC for buprenorphine increased by up to 1.6 and 1.9 fold, and C_{max} and AUC for norbuprenorphine increased by up to 1.6 and 2.0 fold respectively, when sublingual buprenorphine was administered with these PIs. Patients in this study reported increased sedation, and symptoms of opiate excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. It should be noted that atazanavir is both a CYP3A4 and UGT1A1 inhibitor. As such, the drug-drug

interaction potential for buprenorphine with CYP3A4 inhibitors is likely to be dependent on the route of administration as well as the specificity of enzyme inhibition *[see Drug Interactions (7.1)]*.

Effect of CYP3A4 Inducers
The interaction between buprenorphine and CYP3A4 inducers has not been studied.

Effects of Application Site
A study in healthy subjects demonstrated that the pharmacokinetic profile of buprenorphine delivered by BUTRANS 10 mcg/hour is similar when applied to the upper outer arm, upper chest, upper back, or the side of the chest *[see Dosage and Administration (2.5)]*.

The reapplication of BUTRANS 10 mcg/hour after various rest periods to the same application site in healthy subjects showed that the minimum rest period needed to avoid variability in drug absorption is 3 weeks (21 days) *[see Dosage and Administration (2.5)]*.

Effects of Heat
In a study of healthy subjects, application of a heating pad directly on the BUTRANS 10 mcg/hour system caused a 26% - 55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed. For this reason, instruct patients not to apply heating pads directly to the BUTRANS system during system wear *[see Warnings and Precautions (5.13)]*.

Fever may increase the permeability of the skin, leading to increased buprenorphine concentrations during BUTRANS treatment. As a result, febrile patients are at increased risk for the possibility of BUTRANS-related reactions during treatment with BUTRANS. Monitor patients with febrile illness for adverse effects and consider dose adjustment *[see Warnings and Precautions (5.14)]*. In a crossover study of healthy subjects receiving endotoxin or placebo challenge during BUTRANS 10 mcg/hour wear, the AUC and C_{max} were similar despite a physiologic response of mild fever to endotoxin.

<u>*Special Populations*</u>

Geriatric Patients
Following a single application of BUTRANS 10 mcg/hour to 12 healthy young adults (mean age 32 years) and 12 healthy elderly subjects (mean age 72 years), the pharmacokinetic profile of BUTRANS was similar in healthy elderly and healthy young adult subjects, though the elderly subjects showed a trend toward higher plasma concentrations immediately after BUTRANS removal. Both groups eliminated buprenorphine at similar rates after system removal *[see Use in Specific Populations (8.5)]*.

In a study of healthy young subjects, healthy elderly subjects, and elderly subjects treated with thiazide diuretics, BUTRANS at a fixed dose-escalation schedule (BUTRANS 5 mcg/hour for 3 days, followed by BUTRANS 10 mcg/hour for 3 days and BUTRANS 20 mcg/hour for 7 days) produced similar mean plasma concentration vs. time profiles for each of the three subject groups. There were no significant differences between groups in buprenorphine C_{max} or AUC *[see Use in Specific Populations (8.5)]*.

Pediatric Patients
BUTRANS has not been studied in children and is not recommended for pediatric use.

Gender
In a pooled data analysis utilizing data from several studies that administered BUTRANS 10 mcg/hour to healthy subjects, no differences in buprenorphine C_{max} and AUC or body-weight normalized C_{max} and AUC were observed between males and females treated with BUTRANS.

Renal Impairment
No studies in patients with renal impairment have been performed with BUTRANS.

In an independent study, the effect of impaired renal function on buprenorphine pharmacokinetics after IV bolus and after continuous IV infusion administrations was evaluated. It was found that plasma buprenorphine concentrations were similar in patients with normal renal function and in patients with impaired renal function or renal failure. In a separate investigation of the effect of intermittent

hemodialysis on buprenorphine plasma concentrations in chronic pain patients with end-stage renal disease who were treated with a transdermal buprenorphine product (marketed outside the US) up to 70 mcg/hour, no significant differences in buprenorphine plasma concentrations before or after hemodialysis were observed.

No notable relationship was observed between estimated creatinine clearance rates and steady-state buprenorphine concentrations among patients during BUTRANS therapy.

Hepatic Impairment
The pharmacokinetics of buprenorphine following an IV infusion of 0.3 mg of buprenorphine were compared in 8 patients with mild impairment (Child-Pugh A), 4 patients with moderate impairment (Child-Pugh B) and 12 subjects with normal hepatic function. Buprenorphine and norbuprenorphine exposure did not increase in the mild and moderate hepatic impairment patients.

BUTRANS has not been evaluated in patients with severe (Child-Pugh C) hepatic impairment *[see Dosage and Administration (2.4), Warnings and Precautions (5.10), and Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Buprenorphine administered daily by skin painting to Sprague Dawley rats for 100 weeks at dosages (20, 60, or 200 mg/kg) produced systemic exposures (based on AUC) that ranged from approximately 130 to 350 times that of human subjects administered the maximum recommended human dose (MRHD) of BUTRANS 20 mcg/hour. An increased incidence of benign testicular interstitial cell tumors, considered buprenorphine treatment-related, was observed in male rats compared with concurrent controls. The tumor incidence was also above the highest incidence in the historical control database of the testing facility. These tumors were noted at 60 mg/kg/day and higher at approximately 220 times the proposed MRHD based on AUC. The no observed effect level (NOEL) was 20 mg/kg/day (approximately 140 times the proposed MRHD based on AUC). The mechanism leading to the tumor findings and the relevance to humans is unknown.

Buprenorphine was administered by skin painting to hemizygous Tg.AC mice over a 6-month study period. At the dosages administered daily (18.75, 37.5, 150, or 600 mg/kg/day), buprenorphine was not carcinogenic or tumorigenic at systemic exposure to buprenorphine, based on AUC, of up to approximately 1000 times that of human subjects administered BUTRANS 20 mcg/hour, the MRHD.

Mutagenesis
Buprenorphine was not genotoxic in 3 *in vitro* genetic toxicology studies (bacterial mutagenicity test, mouse lymphoma assay, chromosomal aberration assay in human peripheral blood lymphocytes), and in one *in vivo* mouse micronucleus test.

Impairment of Fertility
BUTRANS (1/4 of a BUTRANS 5 mcg/hour, one BUTRANS 5 mcg/hour, or one BUTRANS 20 mcg/hour every 3 days in males for 4 weeks prior to mating for a total of 10 weeks and in females for 2 weeks prior to mating through gestation day 7) had no effect on fertility or general reproductive performance of rats at AUC-based exposure levels as high as approximately 65 times (females) and 100 times (males) that for human subjects who received BUTRANS 20 mcg/hour, the MRHD.

14 CLINICAL STUDIES

The efficacy of BUTRANS has been evaluated in four 12-week double-blind, controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe chronic low back pain or osteoarthritis using pain scores as the primary efficacy variable. Two of these studies, described below, demonstrated efficacy in patients with low back pain. One study in low back pain failed to show

efficacy. One study in osteoarthritis, that included an active comparator, failed to show efficacy for BUTRANS and the active comparator.

12-Week Study in Opioid-Naïve Patients with Chronic Low Back Pain

A total of 1,024 patients with chronic low back pain who were suboptimally responsive to their non-opioid therapy entered an open-label, dose-titration period for up to four weeks. Patients initiated therapy with three days of treatment with BUTRANS 5 mcg/hour. After three days, if adverse events were tolerated but the pain persisted (≥ 5 on an 11-point, 0 to 10 Numerical Rating Scale), the dose was increased to BUTRANS 10 mcg/hour. If adverse effects were tolerated but adequate analgesia was not reached, the dose was increased to BUTRANS 20 mcg/hour for an additional 10-12 days. Patients who achieved adequate analgesia and tolerable adverse effects on BUTRANS were then randomized to remain on their titrated dose of BUTRANS or matching placebo. Fifty-three percent of the patients who entered the open-label titration period were able to titrate to a tolerable and effective dose and were randomized into a 12-week, double-blind treatment period. Twenty-three percent of patients discontinued due to an adverse event from the open-label titration period and 14% discontinued due to lack of a therapeutic effect. The remaining 10% of patients were dropped due to various administrative reasons.

During the first seven days of double-blind treatment patients were allowed up to two tablets per day of immediate-release oxycodone 5 mg as supplemental analgesia to minimize opioid withdrawal symptoms in patients randomized to placebo. Thereafter, the supplemental analgesia was limited to either acetaminophen 500 mg or ibuprofen 200 mg at a maximum of four tablets per day. Sixty-six percent of the patients treated with BUTRANS completed the 12-week treatment compared to 70% of the patients treated with placebo. Of the 256 patients randomized to BUTRANS, 9% discontinued due to lack of efficacy and 16% due to adverse events. Of the 283 patients randomized to placebo, 13% discontinued due to lack of efficacy and 7% due to adverse events.

Of the patients who were randomized, the mean pain (SE) NRS scores were 7.2 (0.08) and 7.2 (0.07) at screening and 2.6 (0.08) and 2.6 (0.07) at pre-randomization (beginning of double-blind phase) for the BUTRANS and placebo groups, respectively.

The score for average pain over the last 24 hours at the end of the study (Week 12/Early Termination) was statistically significantly lower for patients treated with BUTRANS compared with patients treated with placebo. The proportion of patients with various degrees of improvement, from screening to study endpoint, is shown in Figure 3 below.

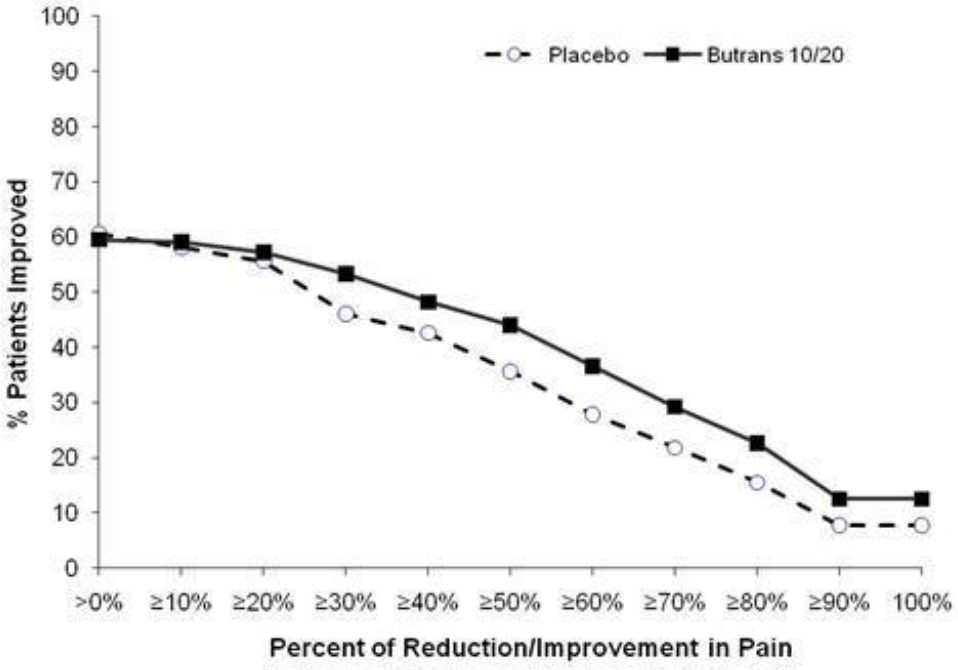


Figure 3: Percent Reduction in Pain Intensity

12-Week Study in Opioid-Experienced Patients with Chronic Low Back Pain

One thousand one hundred and sixty (1,160) patients on chronic opioid therapy (total daily dose 30-80 mg morphine equivalent) entered an open-label, dose-titration period with BUTRANS for up to 3 weeks, following taper of prior opioids. Patients initiated therapy with BUTRANS 10 mcg/hour for three days. After three days, if the patient tolerated the adverse effects, the dose was increased to BUTRANS 20 mcg/hour for up to 18 days. Patients with adequate analgesia and tolerable adverse effects on BUTRANS 20 mcg/hour were randomized to remain on BUTRANS 20 mcg/hour or were switched to a low-dose control (BUTRANS 5 mcg/hour) or an active control. Fifty-seven percent of the patients who entered the open-label titration period were able to titrate to and tolerate the adverse effects of BUTRANS 20 mcg/hour and were randomized into a 12-week double-blind treatment phase. Twelve percent of patients discontinued due to an adverse event and 21% discontinued due to lack of a therapeutic effect during the open-label titration period.

During the double-blind period, patients were permitted to take ibuprofen (200 mg tablets) or acetaminophen (500 mg tablets) every 4 hours as needed for supplemental analgesia (up to 3200 mg of ibuprofen and 4 grams of acetaminophen daily). Sixty-seven percent of patients treated with BUTRANS 20 mcg/hour and 58% of patients treated with BUTRANS 5 mcg/hour completed the 12-week treatment. Of the 219 patients randomized to BUTRANS 20 mcg/hour, 11% discontinued due to lack of efficacy and 13% due to adverse events. Of the 221 patients randomized to BUTRANS 5 mcg/hour, 24% discontinued due to lack of efficacy and 6% due to adverse events. Of the patients who were able to be randomized in the double-blind period, the mean pain (SE) NRS scores were 6.4 (0.08) and 6.5 (0.08) at screening and were 2.8 (0.08) and 2.9 (0.08) at pre-randomization (beginning of Double-Blind Period) for the BUTRANS 5 mcg/hour and BUTRANS 20 mcg/hour, respectively.

The score for average pain over the last 24 hours at Week 12 was statistically significantly lower for subjects treated with BUTRANS 20 mcg/hour compared to subjects treated with BUTRANS 5 mcg/hour. A higher proportion of BUTRANS 20 mcg/hour patients (49%) had at least a 30% reduction in pain score from screening to study endpoint when compared to BUTRANS 5 mcg/hour patients (33%). The proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 4 below.

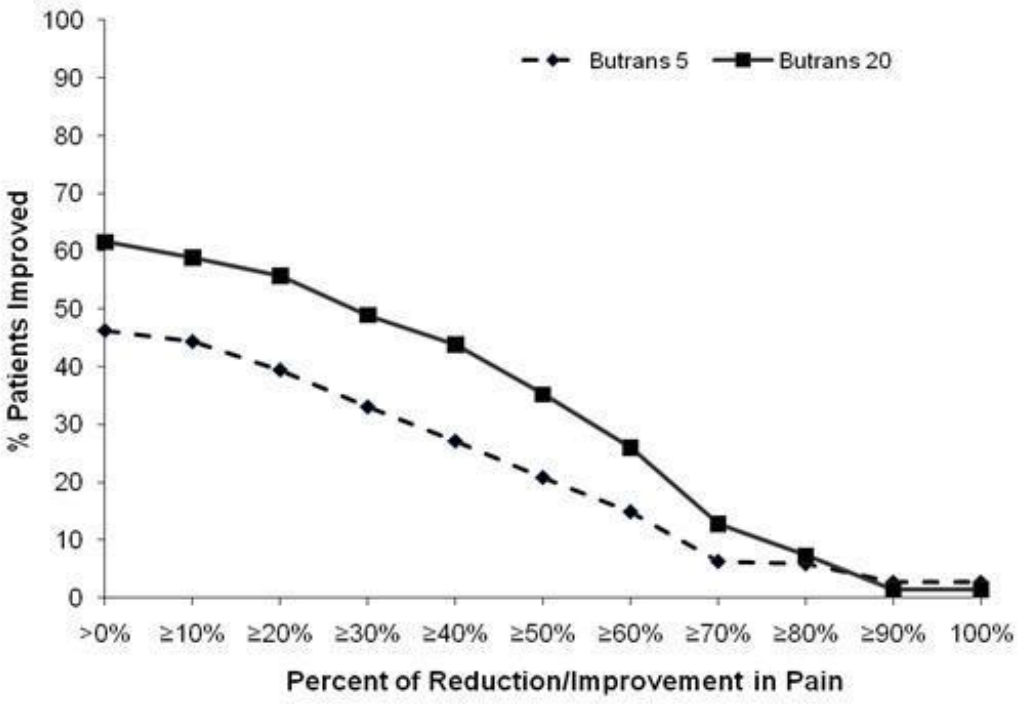


Figure 4: Percent Reduction in Pain Intensity

16 HOW SUPPLIED/STORAGE AND HANDLING

BUTRANS (buprenorphine) Transdermal System is supplied in cartons containing 4 individually-packaged systems and a pouch containing 4 Patch-Disposal Units.

BUTRANS 5 mcg/hour Transdermal System, 4-count carton
NDC 59011-750-04

BUTRANS 10 mcg/hour Transdermal System, 4-count carton
NDC 59011-751-04

BUTRANS 20 mcg/hour Transdermal System, 4-count carton
NDC 59011-752-04

Store at 25°C (77°F); excursions permitted between 15°C - 30°C (59°F - 86°F).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Abuse Potential
Inform patients that BUTRANS contains buprenorphine, a Schedule III controlled substance that is subject to abuse. Instruct patients not to share BUTRANS with others and to take steps to protect BUTRANS from theft or misuse.

Life-Threatening Respiratory Depression
Discuss the risk of respiratory depression with patients, explaining that the risk is greatest when starting BUTRANS or when the dose is increased. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Accidental Exposure
Instruct patients to take steps to store BUTRANS securely. Accidental exposure, especially in children, may results in serious harm or death. Advise patients to dispose of unused BUTRANS folding in half

and flushing down the toilet.

Risks from Concomitant Use of Alcohol and other CNS Depressants
Inform patients that the concomitant use of alcohol with BUTRANS can increase the risk of life-threatening respiratory depression.

Inform patients that potentially serious additive effects may occur if BUTRANS is used with other CNS depressants, and not to use such drugs unless supervised by a health care provider.

Important Administration Instructions

Instruct patients how to properly use BUTRANS, including the following:

1. To carefully follow instructions for the application, removal, and disposal of BUTRANS. Each week, apply BUTRANS to a different site based on the 8 described skin sites, with a minimum of 3 weeks between applications to a previously used site.
2. To apply BUTRANS to a hairless or nearly hairless skin site. If none are available, instruct patients to clip the hair at the site and not to shave the area. Instruct patients not to apply to irritated skin. If the application site must be cleaned, use clear water only. Soaps, alcohol, oils, lotions, or abrasive devices should not be used. Allow the skin to dry before applying BUTRANS.

Hypotension
Inform patients that BUTRANS may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

Driving or Operating Heavy Machinery
Inform patients that BUTRANS may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Anaphylaxis
Inform patients that anaphylaxis has been reported with ingredients contained in BUTRANS. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy
Advise female patients that BUTRANS can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Distributed by: Purdue Pharma L.P., Stamford, CT 06901-3431
Manufactured by: LTS Lohmann Therapie-Systeme AG, Andernach, Germany

U.S. Patent Numbers 5681413; 5804215; 6264980; 6315854; 6344211; RE41408; RE41489; RE41571.

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Medication Guide
BUTRANS® (BYOO-trans)
(buprenorphine) Transdermal System, CIII

BUTRANS is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to treat moderate to severe around-the-clock pain.

Important information about BUTRANS:

- Get emergency help right away if you take too much BUTRANS (overdose). BUTRANS overdose can cause life-threatening breathing problems that can lead to death.
- Never give anyone else your BUTRANS. They could die from taking it. Store BUTRANS away from children and in a safe place to prevent stealing or abuse. Selling or giving away BUTRANS is against the law.

Do not use BUTRANS if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before applying BUTRANS, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- heart rhythm problems (Long QT syndrome)
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you:

- have a fever.
- **are pregnant or planning to become pregnant.** BUTRANS may harm your unborn baby.
- **are breastfeeding.** BUTRANS passes into breast milk and may harm your baby.
- are taking prescription or over-the-counter medicines, vitamins, or herbal supplements.

While using BUTRANS:

- Do not change your dose. Apply BUTRANS exactly as prescribed by your healthcare provider.
- See the detailed Instructions for Use for information about how to apply and dispose of the BUTRANS patch.
- Do not apply a BUTRANS patch if the pouch seal is broken, or the patch is cut, damaged, or changed in any way.
- Do not apply more than 1 patch at the same time unless your healthcare provider tells you to.
- You should wear 1 BUTRANS patch continuously for 7 days.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop using BUTRANS without talking to your healthcare provider.**

While using BUTRANS Do Not:

- Take hot baths or sunbathe, use hot tubs, saunas, heating pads, electric blankets, heated waterbeds, or tanning lamps. These can cause an overdose that can lead to death.
- Drive or operate heavy machinery,until you know how BUTRANS affects you. BUTRANS can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

The possible side effects of BUTRANS are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, itching, redness or rash where the patch is applied. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, or you are feeling faint.

These are not all the possible side effects of BUTRANS. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**
Distributed by: Purdue Pharma L.P., Stamford, CT 06901-3431, **www.purduepharma.com or call 1-888-726-7535**

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issue: July 2012

Instructions for Use

Butrans® (BYOO-trans) CIII
(buprenorphine)
Transdermal System

Be sure that you read, understand, and follow these Instructions for Use before you use Butrans. Talk to your doctor or pharmacist if you have any questions.

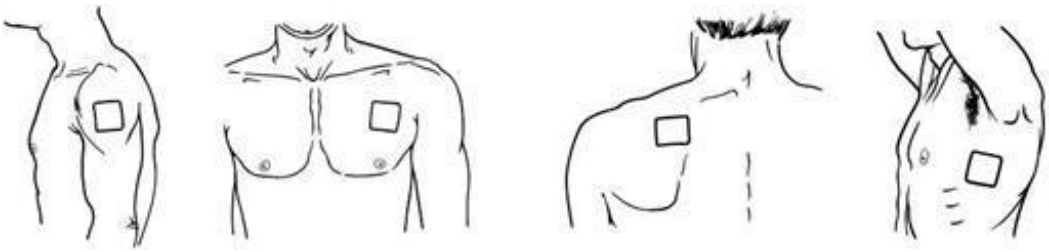
Before Applying Butrans:

- Do not use soap, alcohol, lotions, oils, or other products to remove any leftover medicine gel from a patch because this may cause more Butrans to pass through the skin.
- Each patch is sealed in its own protective pouch. Do not remove a patch from the pouch until you are ready to use it.
- Do not use a patch if the seal on the protective pouch is broken or if the patch is cut, damaged or changed in any way.
- Butrans patches are available in 3 different strengths and patch sizes. Make sure you have the right strength patch that has been prescribed for you.

Where to apply Butrans:

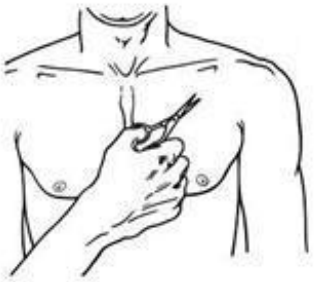
- Butrans should be applied to the **upper outer arm, upper chest, upper back, or the side of the chest** (See Figure 1). These 4 sites (located on both sides of the body) provide 8 possible Butrans application sites. You should change the skin site where you apply Butrans each week, making sure that at least 3 weeks (21 days) pass before you re-use the same skin site.

Figure 1



- Apply Butrans to **a hairless or nearly hairless skin site**. If needed, you can clip the hair at the skin site (See Figure 2). Do not shave the area. The skin site should not be irritated. **Use only water to clean** the application site. You should not use soaps, alcohol, oils, lotions, or abrasive devices. Allow the skin to dry before you apply the patch.

Figure 2



- The skin site should be free of cuts and irritation (rashes, swelling, redness, or other skin problems).

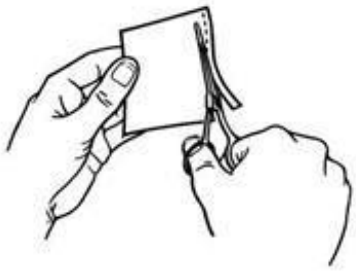
When to apply a new patch:

- When you apply a new patch, write down the date and time that the patch is applied. Use this to remember when the patch should be removed.
- Change the patch at the same time of day, one week (exactly 7 days) after you apply it.
- After removing and disposing of the patch, write down the time it was removed and how it was disposed.

How to apply Butrans:

- If you are wearing a patch, remember to remove it before applying a new one.
- Each patch is sealed in its own protective pouch.
- Use scissors to cut open the pouch along the dotted line (See Figure 3) and remove the patch. Do not remove the patch from the pouch until you are ready to use it. Do not use patches that have been cut or damaged in any way.

Figure 3



- Hold the patch with the protective liner facing you.
- Gently bend the patch (See Figures 4a and 4b) along the faint line and slowly peel the larger portion of the liner, which covers the sticky surface of the patch.

Figure 4a

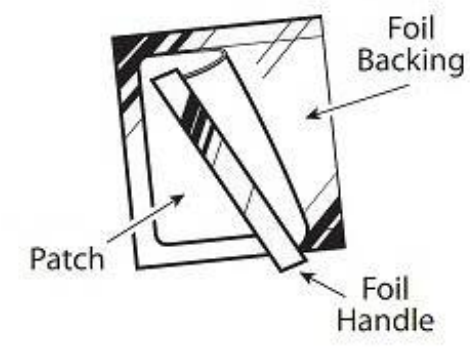
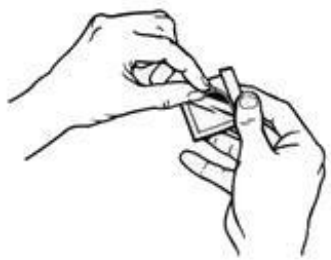
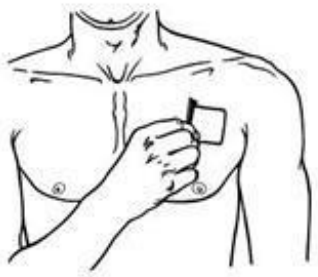


Figure 4b



- Do not touch the sticky side of the patch with your fingers.
- Using the smaller portion of the protective liner as a handle (See Figure 5), apply the sticky side of the patch to one of the 8 body locations described above (see **Where to apply Butrans?**).

Figure 5



- While still holding the sticky side down, gently fold back the smaller portion of the patch. Grasp an edge of the remaining protective liner and slowly peel it off (See Figure 6).

Figure 6

- Press the entire patch firmly into place with the palm (See Figure 7) of your hand over the patch, for about 15 seconds. Do not rub the patch.

Figure 7

- Make sure that the patch firmly sticks to the skin.
- Go over the edges with your fingers to assure good contact around the patch.
- Always wash your hands after applying or handling a patch.
- After the patch is applied, write down the date and time that the patch is applied. Use this to remember when the patch should be removed.

If the patch falls off right away after applying, throw it away and put a new one on at a different skin site (see **Disposing of Butrans Patch**).

If a patch falls off, do not touch the sticky side of the patch with your fingers. A new patch should be applied to a different site. **Patches that fall off should not be re-applied**. They must be thrown away correctly.

If the edges of the Butrans patch start to loosen:

- Apply first aid tape only to the edges of the patch.
- If problems with the patch not sticking continue, cover the patch with special see-through adhesive dressings (for example Bioclusive or Tegaderm).
  - Remove the backing from the transparent adhesive dressing and place it carefully and completely over the Butrans patch, smoothing it over the patch and your skin.
- **Never cover a Butrans patch with any other bandage or tape. It should only be covered with a special see-through adhesive dressing. Talk to your doctor or pharmacist about the kinds of dressing that should be used.**

If your patch falls off later, but before 1 week (7 days) of use, throw it away properly (see **Disposing of a Butrans Patch**) and apply a new patch at a different skin site. Be sure to let your doctor know that this has happened. Do not replace the new patch until 1 week (7 days) after you put it on (or as directed by your doctor).

Disposing of Butrans Patch:

Butrans patches must be disposed of by flushing them down the toilet or using the Patch-Disposal Unit.

To flush your Butrans patches down the toilet:
Remove your Butrans patch, fold the sticky sides of a used patch together (See Figure 8) and flush it down the toilet right away.

Figure 8

When disposing of unused Butrans patches you no longer need, remove the leftover patches from their protective pouch and remove the protective liner. Fold the patches in half with the sticky sides together, and flush the patches down the toilet.

Do not flush the pouch or the protective liner down the toilet. These items can be thrown away in the trash.

If you prefer not to flush the used patch down the toilet, you must use the Patch-Disposal Unit provided to you to discard the patch.

Never put used Butrans patches in the trash without first sealing them in the Patch-Disposal Unit.

To dispose of Butrans patches in household trash using the Patch-Disposal Unit:
Remove your patch and follow the directions printed on the Patch-Disposal Unit (See Figure 9) or see complete instructions below. **Use one Patch-Disposal Unit for each patch.**

Figure 9

1. Peel back the disposal unit liner to show the sticky surface (See Figure 10).

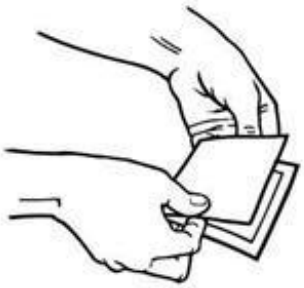
Figure 10

2. Place the sticky side of the used or unused patch to the indicated area on the disposal unit (See Figure 11).

Figure 11

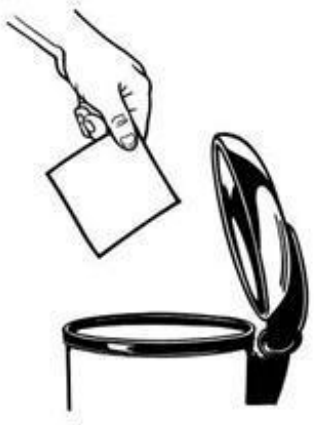
3. Close the disposal unit by folding the sticky sides together (See Figure 12). Press firmly and smoothly over the entire disposal unit so that the patch is sealed within.

Figure 12



4. The closed disposal unit, with the patch sealed inside may be thrown away in the trash (See Figure 13).

Figure 13



Do not put unused patches in household trash without first sealing them in the Patch-Disposal Unit.

Always remove the leftover patches from their protective pouch and remove the protective liner. The pouch and liner can be disposed of separately in the trash and should not be sealed in the Patch-Disposal Unit.

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A-S Medication Solutions
Libertyville, IL 60048

Issued: July 2012

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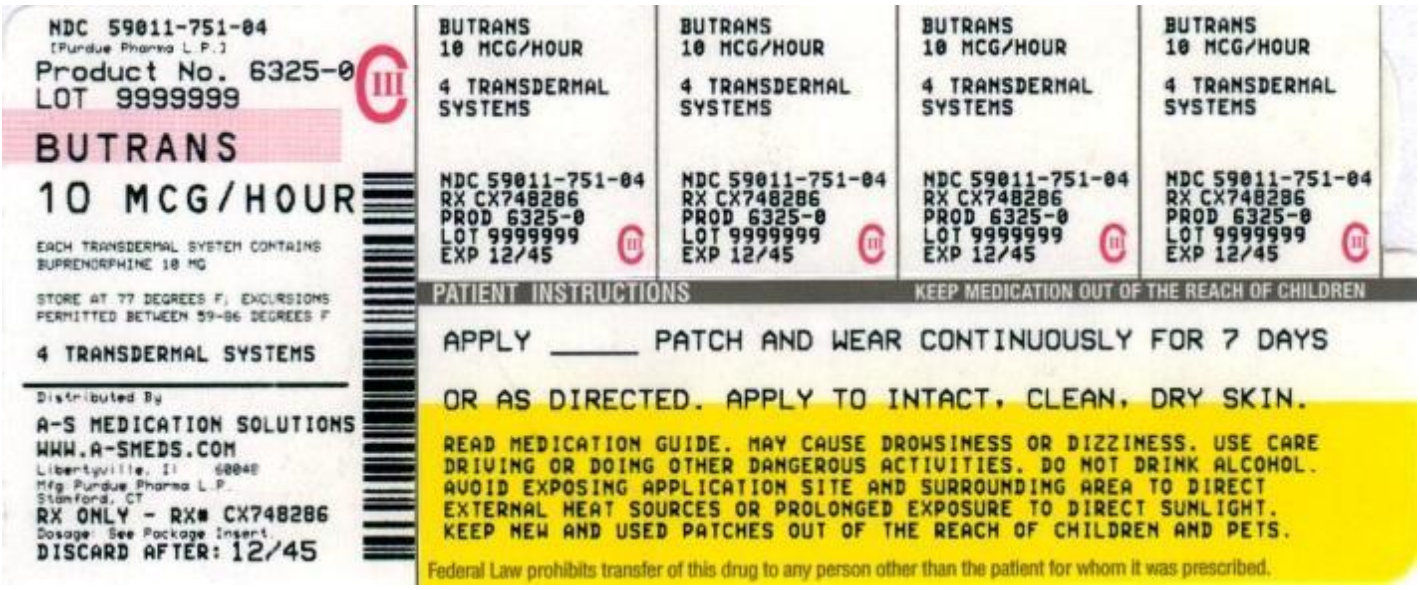
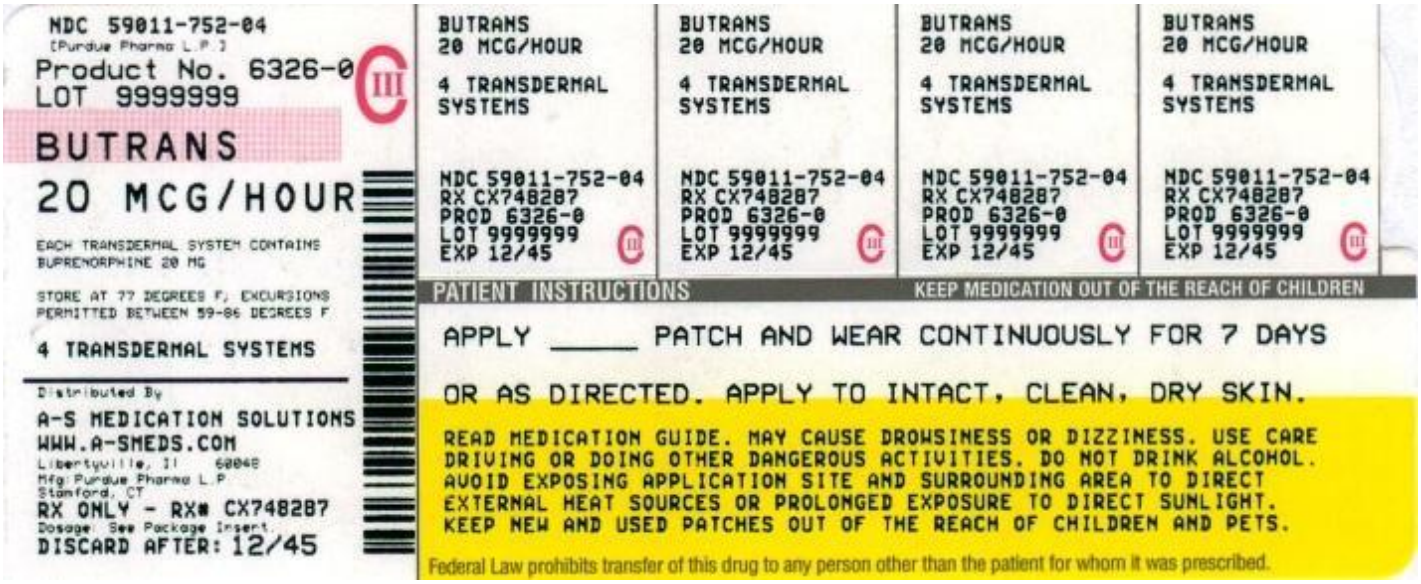
Tegaderm is a trademark of 3M.

Butrans® 10 mcg
NDC 54569-6325-0



Butrans® 20 mcg
NDC 54569-6326-0



BUTRANS

buprenorphine patch, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:54569-6325(NDC:59011-751)
Route of Administration	TRANSDERMAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
buprenorphine (buprenorphine)	buprenorphine	10 ug in 1 h

Inactive Ingredients

Ingredient Name	Strength
ETHYL LEVULINATE	
OLEYL OLEATE	
POVIDONE	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54569-6325-0	4 in 1 CARTON		
1		1 in 1 POUCH		
1		168 h in 1 PATCH		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021306	02/14/2011	

BUTRANS

buprenorphine patch, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:54569-6326(NDC:59011-752)
Route of Administration	TRANSDERMAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
buprenorphine (buprenorphine)	buprenorphine	20 ug in 1 h

Inactive Ingredients

Ingredient Name	Strength
ETHYL LEVULINATE	
OLEYL OLEATE	
POVIDONE	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54569-6326-0	4 in 1 CARTON		
1		1 in 1 POUCH		
1		168 h in 1 PATCH		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021306	02/14/2011	

Labeler - A-S Medication Solutions LLC (830016429)

Establishment

Name	Address	ID/FEI	Business Operations
A-S Medication Solutions LLC		830016429	relabel(54569-6325, 54569-6326)