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: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; and NEONATAL OPIOID WITHDRAWL SYNDROME

See full prescribing information for complete boxed warning.

- **BUTRANS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patients risk before prescribing, and monitor for development of these behaviors or conditions. (5.1, 10)**
- **Serious, life-threatening or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients on proper administration of BUTRANS to reduce the risk. (5.2)**
- **Accidental exposure to BUTRANS, especially in children, can result in fatal overdose of buprenorphine. (5.2)**
- **Prolonged use of BUTRANS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	04/2014
Indications and Usage (1)	04/2014
Dosage and Administration (2)	04/2014
Warnings and Precautions (5)	04/2014

----------INDICATIONS AND USAGE----------

BUTRANS is a partial opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. (1)

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve BUTRANS for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- BUTRANS is not indicated as an as-needed (prn) analgesic. (1)

----------DOSAGE AND ADMINISTRATION----------

- BUTRANS doses of 10, 15, and 20 mcg/hour are for opioid-experienced patients only. (2.1)
- For opioid-naïve patients, initiate with a 5 mcg/hour patch. (2.1)
- 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)

----------DOSAGE FORMS AND STRENGTHS----------

Transdermal system: 5 mcg/hour, 10 mcg/hour, 15 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----------

- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs because of additive pharmacological effects. (5.4)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk of respiratory depression. (5.5, 5.6)
- 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----------

- Interaction with benzodiazepines: May increase buprenorphine-induced respiratory depression. Monitor patients on concurrent therapy closely. (7.1)
- CYP3A4 inhibitors/inducers: Initiating CYP3A4 inhibitors or discontinuing CYP3A4 inducers may result in an increase in buprenorphine plasma concentrations. Closely monitor patients starting CYP3A4 inhibitors or stopping CYP3A4 inducers for respiratory depression. (7.3)

----------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: 04/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Full Prescribing Information

WARNING: ADDICTION, ABUSE and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; and NEONATAL OPIOID WITHDRAWAL SYNDROME

Addiction, Abuse, and Misuse
BUTRANS® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing BUTRANS, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1) and Overdosage (10)]*.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of BUTRANS. Monitor for respiratory depression, especially during initiation of BUTRANS or following a dose increase. Misuse or abuse of BUTRANS by chewing, swallowing, snorting or injecting buprenorphine extracted from the transdermal system will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death *[see Warnings and Precautions (5.2)]*.

Accidental Exposure
Accidental exposure to even one dose of BUTRANS, especially by children, can result in a fatal overdose of buprenorphine *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of BUTRANS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

BUTRANS is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risk of overdose and death with extended-release opioid formulations, reserve BUTRANS for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

- BUTRANS is not indicated as an as-needed (prn) analgesic

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

BUTRANS should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

BUTRANS doses of 10, 15, and 20 mcg/hour are for opioid-experienced patients only.

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience and risks factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with BUTRANS *[see Warnings and Precautions (5.2)]*.

BUTRANS is for transdermal use (on intact skin) only. Each BUTRANS patch 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.

Use of BUTRANS as the First Opioid Analgesic
Initiate treatment with BUTRANS with a 5 mcg/hour patch.

Conversion from Other Opioids to BUTRANS
Discontinue all other around-the-clock opioid drugs when BUTRANS therapy is initiated.

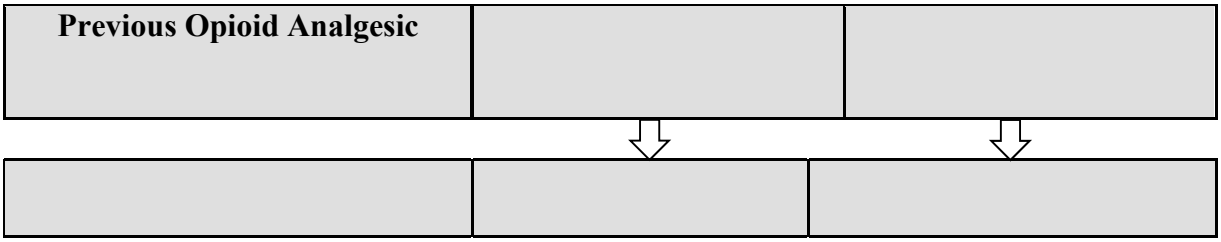
There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids.

Prior Total Daily Dose of Opioid Less than 30 mg of Oral Morphine Equivalents per Day:
Initiate treatment with BUTRANS 5 mcg/hour at the next dosing interval (see Table 1 below, middle column).

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 at the next dosing interval (see Table 1 below, right column). 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



Conversion from Methadone to BUTRANS
Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

2.2 Titration and Maintenance of Therapy
Individually titrate BUTRANS to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving BUTRANS to assess the maintenance of pain control and the relative incidence of adverse reactions, and monitor for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

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 achieved within 72 hours, BUTRANS dosage may be adjusted every 3 days. Dose adjustments may be made in 5 mcg/hour or 10 mcg/hour increments by using no more than two patches of the 5 mcg/hour or 10-mcg/hour system(s). The total dose from all patches should not exceed 20 mcg/hour. For the use of two patches, patients should be instructed to remove their current patch, and apply the two new patches adjacent to one another at a different application site *[see Dosage and Administration (2.5)]*.

Patients who experience breakthrough pain may require dosage adjustment increase of BUTRANS, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the BUTRANS dose.

If unacceptable opioid-related adverse reactions are observed, the subsequent doses 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. See the Instructions for Use for step-by-step instructions for applying BUTRANS.

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.

Incidental exposure of the BUTRANS patch to water, such as while bathing or showering is acceptable based on experience during clinical studies.

If problems with adhesion of BUTRANS occur, the edges may be taped with first aid tape. If problems with lack of adhesion continue, the patch may be covered with waterproof or semipermeable adhesive dressings suitable for 7 days of wear.

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

When changing the system, instruct patients to remove BUTRANS and dispose of it properly *[see Dosage and Administration (2.6)]*.

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.

2.6 Disposal Instructions

Patients should refer to the Instructions for Use for proper disposal of BUTRANS. Dispose of used and unused patches by following the instructions on the Patch-Disposal Unit that is packaged with the BUTRANS patches.

Alternatively, patients can dispose of used patches by folding the adhesive side of the patch to itself, then flushing the patch down the toilet immediately upon removal. Unused patches should be removed from their pouches, the protective liners removed, the patches folded so that the adhesive side of the patch adheres to itself, and immediately flushed down the toilet.

Patients should dispose of any patches remaining from a prescription as soon as they are no longer needed.

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 four 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 15 mcg/hour Transdermal System (dimensions: 59 mm by 72 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 Addiction, Abuse, and Misuse

BUTRANS contains buprenorphine, a Schedule III controlled substance. As an opioid, BUTRANS exposes users to the risks of addiction, abuse, and misuse. As modified-release

products such as BUTRANS deliver the opioid over an extended period of time, there is a greater risk for overdose and death, due to the larger amount of buprenorphine present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed BUTRANS and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused *[see Drug Abuse and Dependence (9)]*.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing BUTRANS, and monitor all patients receiving BUTRANS for the development of these behaviors or conditions. Risks are 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). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as BUTRANS, but use in such patients necessitates intensive counseling about the risks and proper use of BUTRANS, along with intensive monitoring for signs of addiction, abuse, or misuse.

Abuse or misuse of BUTRANS by placing it in the mouth, chewing it, swallowing it, or using it in ways other than indicated may cause choking, overdose and death *[see Overdosage (10)]*.

Opioid agonists such as BUTRANS are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing BUTRANS. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. 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

Serious, life threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression, from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. 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)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

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.

To reduce the risk of respiratory depression, proper dosing and titration of BUTRANS are essential *[see Dosage and Administration (2)]*. Overestimating the BUTRANS dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental exposure to BUTRANS, especially in children, can result in respiratory depression and death due to an overdose of buprenorphine.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of BUTRANS during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid 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 opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

5.4 Interactions with Central Nervous System Depressants

Hypotension, profound sedation, coma, respiratory depression, and death may result if BUTRANS is used concomitantly with alcohol or other (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, 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, evaluate the patient's use, of alcohol or illicit drugs that cause CNS depression. If the decision to begin BUTRANS therapy is made, start with BUTRANS 5mcg/hour patch, monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.2)]*.

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. 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)]*.

5.6 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.

5.7 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 Dosage and Administration (2.2) and 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 (7.2)]*. 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 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.

5.18 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 serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- QTc Prolongation *[see Warnings and Precautions (5.7)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Hypotensive Effects *[see Warnings and Precautions (5.8)]*
- Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- 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 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.

7.2 CNS Depressants

The concomitant use of BUTRANS with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and BUTRANS for signs of respiratory depression, sedation, and hypotension. When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Dosage and Administration (2.2) and Warnings and Precautions (5.4)]*.

7.3 Drugs Affecting Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4 and 2D6

Because the CYP3A4 isoenzyme plays a major role in the metabolism of buprenorphine, drugs that inhibit CYP3A4 activity may cause decreased clearance of buprenorphine which could lead to an increase in buprenorphine plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of CYP2D6 and 3A4 inhibitors. If co-administration with BUTRANS is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

Inducers of CYP3A4

CYP450 3A4 inducers may induce the metabolism of buprenorphine and, therefore, may cause increased clearance of the drug which could lead to a decrease in buprenorphine plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to buprenorphine.

After stopping the treatment of a CYP3A4 inducer, as the effects of the inducer decline, the buprenorphine plasma concentration will increase which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. If co-administration or discontinuation of a CYP3A4 inducer with BUTRANS is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

7.4 Muscle Relaxants

Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and BUTRANS for signs of respiratory depression that may be greater than otherwise expected.

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

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as

poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*.

Teratogenic Effects - Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. BUTRANS should be used during pregnancy only if the potential benefit justifies the potential risk to 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
Opioids cross the placenta and may produce respiratory depression in neonates. BUTRANS is not for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics can prolong labor through actions that 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.

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)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
BUTRANS contains buprenorphine, a Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. BUTRANS can be abused and is subject to misuse, addiction and criminal diversion *[see Warnings and Precautions (5.1)]*.

9.2 Abuse

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 to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of 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, like other opioids, can 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.

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

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 (5.4) and Drug Interactions (7.2)]*. Intentional compromise of 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 (8.1)]*.

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.

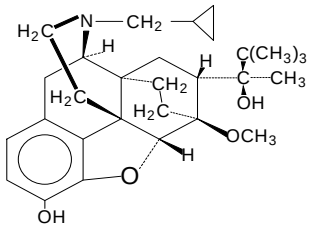
Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. High doses of naloxone, 10-35 mg/70 kg, may be of limited value in the management of buprenorphine overdose. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride (a respiratory 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)- α-(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-α-methyl-, [5α, 7α, (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

Four different strengths of BUTRANS are available: 5, 10, 15, and 20 mcg/hour (Table 5). The proportion of buprenorphine mixed in the adhesive matrix is the same in each of the four 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	Active Surface	Total Buprenorphine

Rate (mcg/hour)	Area (cm^2)	Content (mg)
BUTRANS 5	6.25	5
BUTRANS 10	12.5	10
BUTRANS 15	18.75	15
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.

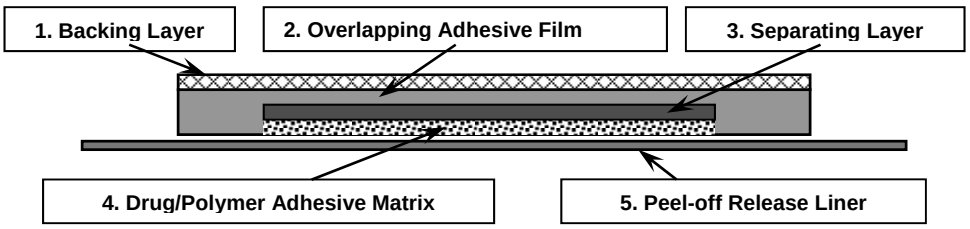


Figure 1: Cross-Section Diagram of BUTRANS (not to scale).

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. The contributions of these actions to its analgesic profile are unclear.

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).

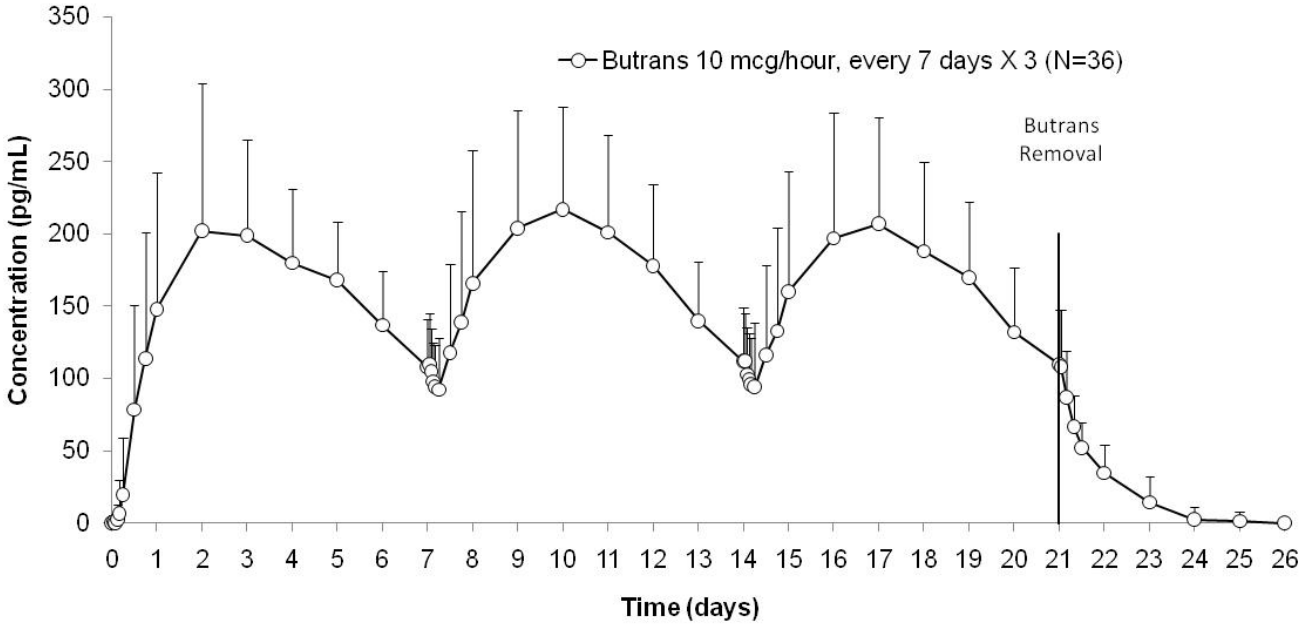


Figure 2
Mean (SD) Buprenorphine Plasma Concentrations Following Three Consecutive Applications of BUTRANS 10 mcg/hour (N = 36 Healthy Subjects)

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.

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).

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.

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.

CSF buprenorphine concentrations appear to be approximately 15-25% of concurrent plasma concentrations.

Metabolism
Buprenorphine metabolism in the skin following BUTRANS application is negligible.

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.

Elimination
Following IV administration, buprenorphine and its metabolites are secreted into bile and excreted in urine.

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.

Following transdermal application, buprenorphine is eliminated via hepatic metabolism, with subsequent biliary excretion and renal excretion of soluble metabolites. 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. 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, leading to increased plasma concentrations.

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 (7.3)]*.

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 (7.3)]*.

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

Specific Populations

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 and one study in osteoarthritis did not show a statistically significant pain reduction for either BUTRANS or the respective active comparators.

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, 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 BUTRANS10 or 20 mcg/hour 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.

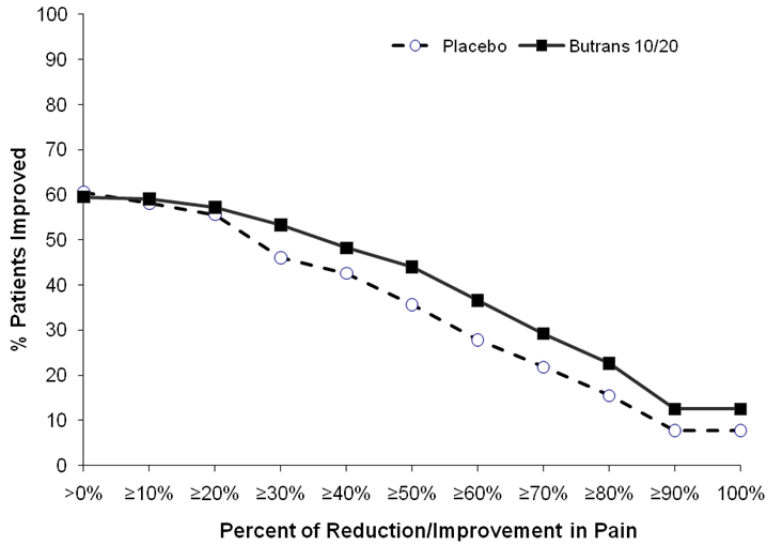


Figure 3: Percent Reduction in Pain Intensity

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.

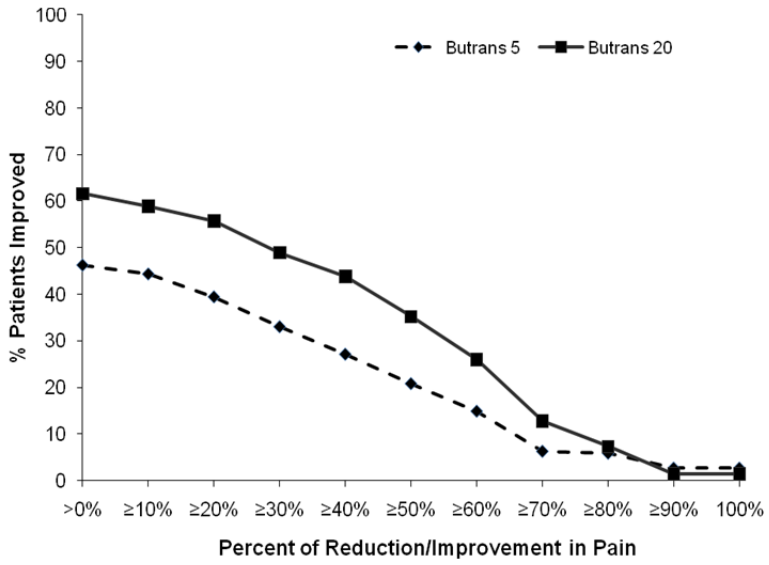


Figure 4: Percent Reduction in Pain Intensity

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 15 mcg/hour Transdermal System, 4-count carton
NDC 59011-758-04

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

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Addiction, Abuse, and Misuse
Inform patients that the use of BUTRANS, even when taken as recommended, can result in addiction, abuse, and misuse, which could lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share BUTRANS with others and to take steps to protect BUTRANS from theft or misuse.

Life-threatening Respiratory Depression
Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting BUTRANS or when the dose is increased, and that it can occur even at recommended doses *[see Warnings and Precaution (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Exposure
Inform patients that accidental exposure, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store BUTRANS securely and to dispose of unused BUTRANS by folding the patch in half and flushing it down the toilet.

Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that prolonged use of BUTRANS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3)]*.

Interaction with Alcohol and other CNS Depressants
Inform patients that potentially serious additive effects may occur if BUTRANS is used with alcohol or 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.

Disposal

Instruct patients to refer to the Instructions for Use for proper disposal of BUTRANS. Patients can dispose of used or unused BUTRANS patches in the trash by sealing it in the Patch-Disposal Unit, following the instructions on the unit.

Alternatively, instruct patients to dispose of used patches by folding the adhesive side of the patch to itself, then flushing the patch down the toilet immediately upon removal. Unused patches should be removed from their pouches, the protective liners removed, the patches folded so that the adhesive side of the patch adheres to itself, and immediately flushed down the toilet.

Instruct patients to dispose of any patches remaining from a prescription as soon as they are no longer needed.

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.

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 manage pain severe enough to require daily, around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about BUTRANS:

- **Get emergency help right away if you take too much BUTRANS (overdose).** When you first start taking BUTRANS, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- 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.** Prolonged use of BUTRANS during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **are breastfeeding.** BUTRANS passes into breast milk and may harm your baby.
- are taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking BUTRANS with certain other medicines can cause serious side effects.

When 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 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 using does not control your pain.**
- **Do not stop using BUTRANS without talking to your healthcare provider.**
- **To properly dispose of used and unused patches, use the Patch-Disposal Unit or fold in half and flush down the toilet. See the detailed Instructions for Use.**

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 containing alcohol. Using products containing alcohol during treatment with BUTRANS may cause you to overdose and die.

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, light-headedness when changing positions, 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.
Revised: April 2014

Reference ID: 3490097

Butrans® CIII
(buprenorphi
l System

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 healthcare provider or pharmacist if you have any questions.

Before Applying BUTRANS:

- Do not use soap, alcohol, lotions, oils, or other products to remove any leftover adhesive 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 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.

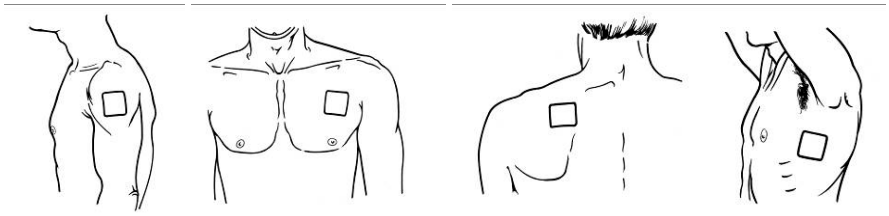


Figure A

- Do not apply more than 1 patch at the same time unless your doctor tells you to. However, if your healthcare provider tells you to do so, you may use 2 patches (5 or 10 mcg/hr **only**), applied at the same site (**See Figure A** for application sites) right next to each other (**See Figure B** for an example of patch position when applying 2 patches). Always apply and remove the two patches together at the same time.

Figure B

- 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.

- Apply BUTRANS to **a hairless or nearly hairless skin site**. If needed, you can clip the hair at the skin site (**See Figure C**). 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.

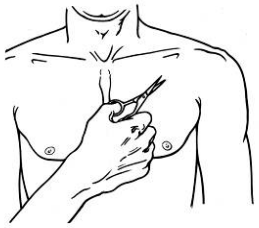


Figure C

- 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.
- If you are using two patches, remember to apply them at the same site right next to each other. Always apply and remove the two patches together at the same time.
- Use scissors to cut open the pouch along the dotted line (**See Figure D**) 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.

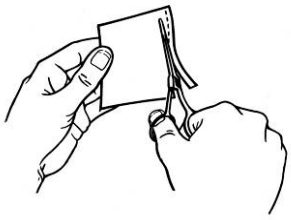


Figure D

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

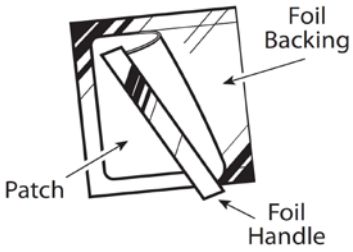


Figure E

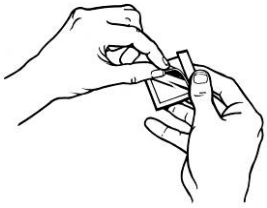


Figure F

- 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 G**), apply the sticky side of the patch to one of the 8 body locations described above (**See "Where to apply BUTRANS"**).

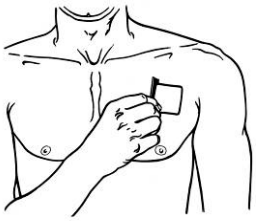


Figure G

- 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 H**).

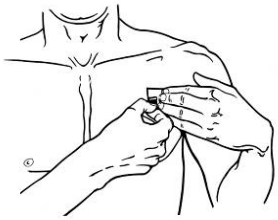


Figure H

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

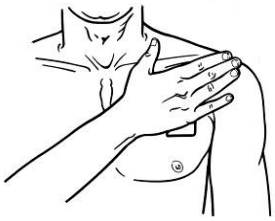


Figure I

- Make sure that the patch firmly sticks to the skin.
- Go over the edges with your fingers to assure good contact around the patch.
- If you are using two patches, follow the steps in this section to apply them right next to each other.
- 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.

Short-term exposure of the BUTRANS patch to water, such as when bathing or showering, is permitted.

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 healthcare provider 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 healthcare provider 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 healthcare provider).

Disposing of BUTRANS Patch:

BUTRANS patches should be disposed of by using the Patch-Disposal Unit. Alternatively, the patches can be flushed down the toilet.

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 J**) or see complete instructions below**. Use one Patch-Disposal Unit for each patch.**

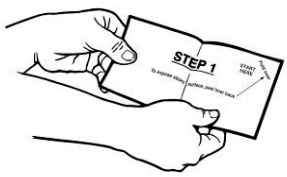


Figure J

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

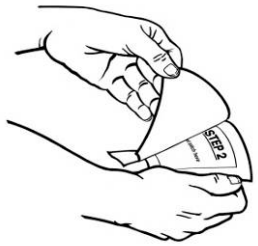


Figure K

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

Figure L

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

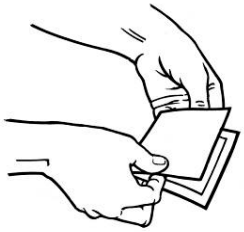


Figure M

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

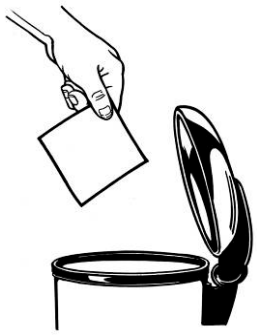


Figure N

Do not put <u>unused</u> 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.

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

Figure O

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.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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