WARNING: ADDICTION, ABUSE and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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 and 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 in 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)].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.4), Drug Interactions (7)].
- Reserve concomitant prescribing of Butrans and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Please read accompanying Full Prescribing Information, including Boxed Warning.
### INDICATIONS AND USAGE

Butrans® (buprenorphine) transdermal system CIII 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.

### WARNINGS AND PRECAUTIONS

#### Addiction, Abuse, and Misuse
- *Butrans contains buprenorphine, a Schedule III controlled substance. Butrans exposes users to the risks of opioid addiction, abuse, and misuse. Because extended-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. Addiction can occur at recommended doses and if the drug is misused or abused.*
- *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 and 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 opioids 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.*
- *Opioids 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.*

#### Prescribing Butrans, the only Schedule III transdermal extended-release opioid
- *As a Schedule III opioid, prescriptions can be:
  - Called in or faxed to your patients’ pharmacy with refills, when appropriate†
  - Filled by mail order pharmacies‡
  - Refilled up to 5 times within 6 months, if authorized, before patients would require a new prescription§
- *Butrans has an abuse potential similar to other Schedule III opioids*
- *Butrans can be abused and is subject to misuse, addiction, and criminal diversion. The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse*
- *Butrans is subject to the same requirements of the class Risk Evaluation and Mitigation Strategy (REMS) for all Extended-Release and Long-Acting (ER/LA) opioid analgesic products

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**7-day, Schedule III Butrans offers the flexibility of 5 dosage strengths**

**To help accommodate the individual treatment needs of your patients, Butrans offers the flexibility of 5 dosage strengths**

<table>
<thead>
<tr>
<th>Butrans 5 mcg/hour</th>
<th>Butrans 7.5 mcg/hour</th>
<th>Butrans 10 mcg/hour</th>
<th>Butrans 15 mcg/hour</th>
<th>Butrans 20 mcg/hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 x 45 mm</td>
<td>58 x 45 mm</td>
<td>68 x 45 mm</td>
<td>72 x 59 mm</td>
<td>77 x 72 mm</td>
</tr>
</tbody>
</table>

*Not shown at actual size.
The maximum Butrans dose is 20 mcg/hour.

- *Each Butrans patch is intended to be worn for 7 days*
- *Do not exceed a dose of one 20 mcg/hour Butrans system due to the risk of QTc interval prolongation*
- *Butrans doses of 7.5, 10, 15, and 20 mcg/hour are only for use in patients who are opioid-experienced and in whom tolerance to an opioid of comparable potency has been established*
  
  – Patients who are opioid-experienced are those receiving, for one week or longer, daily opioid doses up to 80 mg/day of oral morphine or an equianalgesic dose of another opioid

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*Patients should verify with their mail order pharmacy, as policies may vary.
†Refills may vary from state to state, please check with state guidelines.*

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Please see Additional Warnings and Precautions on the following pages.
Considerations for prescribing Butrans

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

INDICATIONS AND USAGE

Butrans® (buprenorphine) transdermal system CIII 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 deaths 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.

Opioids should be prescribed only if expected benefits outweigh risks—

as appropriate—and in combination with non-pharmacologic and non-opioid therapy,

PRIOR to initiating therapy with opioids, and periodically during therapy:

• Work with your patient to set realistic treatment goals, including a plan to discontinue opioid treatment if benefits do not outweigh risks.

• Educate your patient about the realistic benefits and known risks of opioid therapy.

• Discuss patient and clinician responsibilities for managing opioid treatment.

• Evaluate risk factors for opioid-related harms—such as history of overdose, substance use disorder, high opioid dosages, or concurrent benzodiazepine use—and incorporate risk mitigation strategies.

• Review state PDMP data to see if your patient is receiving opioid dosages or dangerous combinations that pose high risk for overdose.

• Consider drug testing* to assess for prescribed opioid medications, other controlled prescription drugs, and illicit drugs.

• Plan to evaluate benefits and harms with your patient within 1 to 4 weeks of starting therapy or dose escalation, and continually thereafter (every 3 months or more frequently).

• Avoid prescribing opioid pain medications and benzodiazepines concurrently whenever possible.

During Butrans therapy, use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.

• Life-Threatening Respiratory Depression

Starting the right patient at the right dose

Initiate the dosing regimen for each patient individually, taking into account the patient’s severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse.

• Butrans doses of 7.5, 10, 15, and 20 mcg/hour are only for use in patients who are opioid experienced and in whom tolerance to an opioid of comparable potency has been established.

• Patients who are opioid-experienced are those receiving, for one week or longer, daily opioid dosages up to 80 mg/day of oral morphine or an equianalgesic dose of another opioid.

• Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.

• Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with 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.

• 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.

• Instruct patients to avoid exposing Butrans to external heat sources, hot water, or prolonged direct sunlight.

ADDITIONAL WARNINGS AND PRECAUTIONS

Life-Threatening Respiratory Depression

• Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended, and if not immediately recognized and treated, may lead to respiratory arrest and death.

• 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 dosage increase. Closely monitor patients for respiratory depression, especially within the first 24–72 hours of initiating therapy with and following dosage increases of Butrans.

• To reduce the risk of respiratory depression, proper dosing and titration of Butrans are essential. Overestimating the Butrans dosage 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.

Please see Additional Warnings and Precautions on the preceding and following pages.

*Not every urine drug test reliably detects synthetic or semisynthetic opioids, such as buprenorphine, especially those designed for in-office use. And many laboratories will report urine drug concentrations below a specified “cut-off” as “negative.” Therefore, ensure that the assay’s sensitivity and specificity are appropriate, and consider the urine drug test’s limitations when interpreting results. PDMP = prescription drug monitoring program.

Please read accompanying Full Prescribing Information, including Boxed Warning.
Butrans® (buprenorphine) transdermal system CIII 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.

Starting the right patient at the right dose (cont.)

For opioid-naïve patients or those whose total daily opioid dose is <30 mg of oral morphine equivalent

- Initiate treatment with Butrans 5 mcg/hour at the next dosing interval

For patients whose total daily opioid dose is 30 to 80 mg of oral morphine equivalents

- 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. Patients may use short-acting analgesics as needed until analgesic efficacy with Butrans is attained.

For patients whose total daily opioid dose is >80 mg of oral morphine equivalents

- Butrans 20 mcg/hour may not provide adequate analgesia. Consider the use of an alternate analgesic

<table>
<thead>
<tr>
<th>Current therapy</th>
<th>Current daily dose*</th>
<th>Recommended starting dose†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-opioid analgesics (e.g., NSAIDS, including COX II inhibitors, or APAP)</td>
<td>Doses within the recommended range</td>
<td>Butrans 5 mcg/hour</td>
</tr>
<tr>
<td>Tramadol</td>
<td>&lt;300 mg</td>
<td>Butrans 5 mcg/hour</td>
</tr>
<tr>
<td></td>
<td>300–400 mg†</td>
<td>Butrans 10 mcg/hour</td>
</tr>
<tr>
<td>Codeine</td>
<td>&lt;90 mg</td>
<td>Butrans 5 mcg/hour</td>
</tr>
<tr>
<td></td>
<td>90–250 mg</td>
<td>Butrans 10 mcg/hour</td>
</tr>
<tr>
<td></td>
<td>&gt;250 mg</td>
<td>Butrans may not be appropriate</td>
</tr>
<tr>
<td>Morphine</td>
<td>&lt;30 mg</td>
<td>Butrans 5 mcg/hour</td>
</tr>
<tr>
<td></td>
<td>30–80 mg</td>
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</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Hydrocodone</td>
<td>&lt;15 mg</td>
<td>Butrans 5 mcg/hour</td>
</tr>
<tr>
<td></td>
<td>15–40 mg</td>
<td>Butrans 10 mcg/hour</td>
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<tr>
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<td>&gt;40 mg</td>
<td>Butrans may not be appropriate</td>
</tr>
</tbody>
</table>

*The opioid dose ranges above were used to approximate morphine equivalents in patients taking other opioids when initiating Butrans in a clinical trial.† Prior to enrollment in this trial, patients’ daily opioid dose was between 30 and 80 mg morphine equivalents.6

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.

Please read accompanying Full Prescribing Information, including Boxed Warning.

Reassess the benefits, risks, and need for continued opioid therapy at each patient visit

Continue opioid therapy only if there is clinically meaningful improvement that outweighs risks to patient safety.

Consider how to discontinue opioid therapy if benefits do not outweigh risks.

Evaluate benefits and harms with patients within 1 to 4 weeks of dose initiation or dose increase, and every 3 months (or more frequently) thereafter.

Because risks of opioids increase with higher doses, prescribers should:
- Use caution when increasing opioid dosages, and increase by the smallest appropriate amount, and reassess benefits and risks for each patient at each dose increase.

Evaluate benefits and risks of continued opioid therapy, weighing factors such as:
- Development of addiction, abuse, or misuse
- Maintenance of pain control and the relative incidence of adverse reactions
- Comorbidities and concomitant medicines that may increase the susceptibility of opioid-associated harms
- Whether opioid therapy is helping your patient meet their treatment goals
- Other pain treatment options with non-pharmacologic and non-opioid therapies, as appropriate
- Consultations with a pain specialist as needed to assist in pain management

If benefits do not outweigh harms of continued therapy, optimize other therapies and work with patients to lower the opioid dose or to taper and discontinue the opioid.

ADDITIONAL WARNINGS AND PRECAUTIONS

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Butrans during pregnancy can result in withdrawal 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. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Avoid pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Please see Additional Warnings and Precautions on the preceding and following pages.
TITRATION & MAINTENANCE

Individually titrate Butrans to a dose that provides adequate analgesia and minimizes adverse reactions.

<table>
<thead>
<tr>
<th>Butrans 5 mcg/hour</th>
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</tr>
</thead>
</table>

Dose adjustments may be made in 5 mcg/hour, 7.5 mcg/hour, or 10 mcg/hour increments by using no more than two patches of the 5 mcg/hour, 7.5 mcg/hour, or 10 mcg/hour systems. The total dose from both patches should not exceed 20 mcg/hour.

Make dose adjustments using 2 of the 5, 7.5, or 10 mcg/hour patches.

<table>
<thead>
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<th>Butrans 10 mcg/hour</th>
</tr>
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</table>

Not shown at actual size.

For the use of 2 patches, instruct patients to remove their current patch and apply the 2 new patches at the same time, adjacent to one another at a different application site.

Addressing breakthrough pain

Patients who experience breakthrough pain may require a dosage increase or may need rescue medication (an immediate-release opioid or non-opioid analgesic).

If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the Butrans dose.

Discontinuation of therapy

When the patient no longer requires therapy with Butrans, use a gradual downward titration of the dose every 7 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, consider introduction of an appropriate immediate-release opioid medication. Do not abruptly discontinue Butrans.

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.

Please read accompanying Full Prescribing Information, including Boxed Warning.
Butrans® (buprenorphine) transdermal system CIII 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.

How to administer Butrans

Instruct patients on Butrans application as follows:

- Butrans is for transdermal use (on intact skin) only. Each Butrans patch is intended to be worn for 7 days
- Apply Butrans immediately after removal from the individually sealed pouch. Do not use Butrans if the pouch seal is broken or the patch is cut, damaged, or changed in any way
- Apply Butrans to the upper outer arm, upper chest, upper back, or the side of the chest. These 4 sites (each present on both sides of the body) provide 8 possible application sites. Rotate Butrans among the 8 described skin sites. After Butrans removal, wait a minimum of 21 days before reapplying to the same skin site

Apply Butrans immediately after removal from the individually sealed pouch. If the buprenorphine-containing adhesive matrix accidentally contacts the skin, wash the area with water. Do not use soap, alcohol, or other solvents to remove the adhesive because they may enhance the absorption of the drug.

ADDITIONAL WARNINGS AND PRECAUTIONS

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.

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.

Risks of Use with Application of External Heat

- Advise patients and their caregivers to avoid chronic exposure of 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. Advise patient 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.

- Apply Butrans to a hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped, not shaved. 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

ADDITIONAL WARNINGS AND PRECAUTIONS

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma and death may result from the concomitant use of Butrans with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

- If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

- Advise both patients and caregivers about the risks of respiratory depression and sedation when Butrans is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.

Please see Additional Warnings and Precautions on the preceding and following pages.
Butrans® (buprenorphine) transdermal system CIII 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.

**Proper disposal**

- Patients should refer to the Instructions for Use for proper disposal of Butrans patches.
- To dispose of used and unused patches in the household trash, patients should be instructed to follow 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.

**ADDITIONAL WARNINGS AND PRECAUTIONS**

**Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients**

- The use of Butrans in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.
- Butrans-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea even at recommended dosages of Butrans.
- Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because 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. Alternatively, consider the use of non-opioid analgesics in these patients.

**Adrenal Insufficiency**

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers.

**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 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.
- 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 I A antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QTc interval.

Please read accompanying Full Prescribing Information, including Boxed Warning.

**Butrans is supplied in cartons containing 4 individually packaged systems and a pouch containing 4 Patch-Disposal Units**

- 4 pouches, each containing a Transdermal System
- 1 envelope containing 4 disposal units

**ADDITIONAL WARNINGS AND PRECAUTIONS**

**Severe Hypotension**

- 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 been compromised by a reduced blood volume or concurrent administration with certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Butrans. In patients with circulatory shock, Butrans may cause vasodilatation that may further reduce cardiac output and blood pressure. Avoid the use of Butrans in patients with circulatory shock.

**Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness**

- In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Butrans may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Butrans.
- 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.

**Hepatotoxicity**

- 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. For patients at increased risk of hepatotoxicity, obtain baseline liver enzyme levels and monitor periodically and during treatment with Butrans.

Please see Additional Warnings and Precautions on the preceding and following pages.
Use in specific populations

**Pregnancy**
- Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with Butrans in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

**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. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly.

**Labor and delivery:** Opioids cross the placenta and may produce respiratory depression in neonates. An opioid antagonist such as naloxone must be available for reversal of opioid-induced respiratory depression in the neonate. Butrans is not recommended for use in women immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate.

**Lactation**
- Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with Butrans.

**Females and Males of Reproductive Potential**
- **Infertility:** Chronic use of opioids may cause reduced fertility in women and men of reproductive potential.

**Pediatric Use**
- The safety and efficacy of Butrans in patients under 18 years of age has not been established.

**Geriatric Use**
- In the clinical program, the incidences of selected Butrans-related adverse events were higher in older subjects. 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.

**Respiratory depression** is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Butrans slowly in geriatric patients and monitor closely for signs of central nervous system depression and respiratory depression.

**Patients with Hepatic Impairment**
- In a study utilizing intravenous buprenorphine, peak plasma levels (C<sub>max</sub>) 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 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.

**ADDITIONAL WARNINGS AND PRECAUTIONS**

**Risks of Use in 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.

**Risks of Use in Patients with Gastrointestinal Conditions**
- Butrans is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The buprenorphine in Butrans may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

**Increased Risk of Seizures in Patients with Seizure Disorders**
- The buprenorphine in Butrans may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Butrans therapy.

**Risks of 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.

**Use in Addiction Treatment**
- Butrans has not been studied and is not approved for use in the management of addictive disorders.

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

References:
7. Steiner DJ, Sitar S, Wen W, et al. Efficacy and safety of the seven-day buprenorphine transdermal system CIII 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.
Butrans® (buprenorphine) transdermal system CIII 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.

Schedule III Butrans—7 days of buprenorphine delivery
- To help accommodate the individual treatment needs of your patients, Butrans offers the flexibility of 5 dosage strengths: 5, 7.5, 10, 15, and 20 mcg/hour
- Each Butrans patch is intended to be worn for 7 days
- Do not exceed a dose of one 20 mcg/hour Butrans system due to the risk of QTc interval prolongation
- Butrans doses of 7.5, 10, 15, and 20 mcg/hour are only for use in patients who are opioid-experienced and in whom tolerance to an opioid of comparable potency has been established
  - Patients who are opioid-experienced are those receiving, for one week or longer, daily opioid doses up to 80 mg/day of oral morphine or an equianalgesic dose of another opioid.

**WARNING: ADDICTION, ABUSE and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

**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 and 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 in 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)].

**Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants**
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.4), Drug Interactions (7)].
- Reserve concomitant prescribing of Butrans and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

For more information, visit Butrans.com

Please see Warnings and Precautions on the preceding pages.

Please read accompanying Full Prescribing Information, including Boxed Warning.

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MR-00183 BUP019 02/17

EXAMPLE ONLY. PLEASE REFER TO THE FULL PRESCRIBING INFORMATION TO DETERMINE APPROPRIATE DOSING. PATCH NOT SHOWN AT ACTUAL SIZE.
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  CIII

Initial U.S. Approval:  1981

WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
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 patient’s risk before prescribing, and monitor for these behaviors and 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 prolonged opioid use is required 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)

• Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)

-----RECENT MAJOR CHANGES-----
Boxed Warning 12/2016
Indications and Usage (1) 12/2016
Dosage and Administration (2) 12/2016
Warnings and Precautions (5) 12/2016

-----INDICATIONS AND USAGE-----
BUTRANS is a partial opioid agonist 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. (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-
• To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)

• BUTRANS doses of 7.5, 10, 15, and 20 mcg/hour are only for use in patients who are opioid experienced and in whom tolerance to an opioid of comparable potency has been established. Patients who are opioid-experienced are those receiving, for one week or longer, daily opioid doses up to 80 mg/day of oral morphine or an equianalgesic dose of another opioid. (2.1)

• Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)

• Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)

• For opioid-naïve patients, initiate treatment 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)

-----CONTRAINDICATIONS-----
• Significant respiratory depression (4)

• Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (4)

• Known or suspected gastrointestinal obstruction, including paralytic ileus (4)

• Hypersensitivity to buprenorphine (4)

-WARNINGS AND PRECAUTIONS--
• Life Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.5)

• Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.6)

• Risk of Prolonged QTc Interval: 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)

• Severe Hypotension: Monitor during dose initiation and titration. Avoid use of BUTRANS in patients with circulatory shock (5.8)

• Risks of Use in Patients with Increased Intracranial Cranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of BUTRANS in patients with impaired consciousness or coma. (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)
FULL PRESCRIBING INFORMATION:

CONTENTS*

WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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--- DRUG INTERACTIONS ---

• Benzodiazepines: May increase buprenorphine-induced respiratory depression. Monitor patients on concurrent therapy closely. (7)

• 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)

• Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue BUTRANS if serotonin syndrome is suspected. (7)

• Mixed Agonist/Antagonist Analgesics: Avoid use with BUTRANS because they may reduce analgesic effect of BUTRANS or precipitate withdrawal symptoms. (7)

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**WARNING: ADDICTION, ABUSE and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

**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 and 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 in 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)].

**Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants**

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.4)].

**Drug Interactions (7)**

- Reserve concomitant prescribing of BUTRANS and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

**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 [see Warnings and Precautions (5.1)], reserve BUTRANS for use in patients with 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 Important Dosage and Administration Information**

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 7.5, 10, 15, and 20 mcg/hour are only for use in patients who are opioid experienced and in whom tolerance to an opioid of comparable potency has been established. Patients who are opioid-experienced are those receiving, for one week or longer, daily opioid doses up to 80 mg/day of oral morphine or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration consistent with individual patients’ treatment goals [see Warnings and Precautions (5.1)].
- Initiate the dosing regimen for each patient individually, taking into account the patient’s severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5.1)].

**Table 1: Initial BUTRANS Dose**

<table>
<thead>
<tr>
<th>Previous Opioid Analgesic Daily Dose (Oral Morphine Equivalent)</th>
<th>&lt;30 mg</th>
<th>30-80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended BUTRANS Starting Dose</td>
<td>5 mcg/hour</td>
<td>10 mcg/hour</td>
</tr>
</tbody>
</table>

**Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with BUTRANS [see Warnings and Precautions (5.2)].**

**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.**

**Instruct patients to avoid exposing BUTRANS to external heat sources, hot water, or prolonged direct sunlight [see Warnings and Precautions (5.14)].**

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

**2.2 Initial Dosage**

**Use of BUTRANS as the First Opioid Analgesic**

- (opioid-naive patients): 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.
patches at the same time, adjacent to one
their current patch, and apply the two new
dosage may be adjusted every 3 days. Dose
increasing the BUTRANS dose.
identify the source of increased pain before
increases after dose stabilization, attempt to
release analgesic. If the level of pain
may require dosage adjustment increase of
BUTRANS or may need rescue medication
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.
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,
7.5 mcg/hour, or 10 mcg/hour increments
by using no more than two patches of the 5
mcg/hour, or 7.5 mcg/hour, or 10 mcg/hour
system(s). The total dose from both patches
should not exceed 20 mcg/hour. For the use
of two patches, instruct patients to remove
their current patch, and apply the two new
patches at the same time, adjacent to one
another at a different application site [see
Dosage and Administration (2.6)].
If unacceptable opioid-related adverse reac-
tions are observed, consider reducing the
dosage. Adjust the dosage to obtain an ap-
propriate balance between the management
of pain and opioid-related adverse reactions.
2.4 Discontinuation of BUTRANS
When the patient no longer requires therapy
with BUTRANS, use a gradual downward
titration of the dose every 7 days, while
monitoring carefully for signs and symptoms
of withdrawal. If the patient develops these
signs or symptoms, consider introduction
of an appropriate immediate-release opioid
medication. Do not abruptly discontinue
BUTRANS.
2.5 Patients with Hepatic
Impairment
BUTRANS has not been evaluated in pa-
tients with severe hepatic impairment. As
BUTRANS is only intended for 7-day applica-
tion, consider use of an alternate analgesic
that may permit more flexibility with the dos-
ing in patients with severe hepatic impair-
ment [see Warnings and Precautions (5.11),
Use in Specific Populations (8.6), and Clinical
Pharmacology (12.3)].
2.6 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 Butler 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 be-
fore 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 irri-
tated 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 show-
ering 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 transder-
mal system properly and place a new
BUTRANS patch on at a different skin site.
• When changing the system, instruct pa-
tients to remove BUTRANS and dispose of
it properly [see Dosage and Administration
(2.7)].
• 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.
2.7 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 re-
maining 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 avail-
able in five strengths:
• BUTRANS 5 mcg/hour Transdermal System
(dimensions: 45 mm by 45 mm)
• BUTRANS 7.5 mcg/hour Transdermal
System (dimensions: 58 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 [see
Warnings and Precautions (5.2)]
• Acute or severe bronchial asthma in an
unmonitored setting or in the absence of
resuscitative equipment [see Warnings and Precautions (5.5)]

- Known or suspected gastrointestinal obstruction, including paralytic ileus [see Warnings and Precautions (5.15)]
- 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 [see Drug Abuse and Dependence (9)]. Because extended-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. Addiction can occur at recommended doses and if the drug is misused or abused.

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 and 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 opioids 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)].

Opioids 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 opioids, even when used as recommended. Respiratory depression, 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 (CO₂) 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 dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of BUTRANS. To reduce the risk of respiratory depression, proper dosing and titration of BUTRANS are essential [see Dosage and Administration (2)]. Overestimating the BUTRANS dosage 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 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. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Use in Specific Populations (8.1), Patients Counseling Information (17)].

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Prolonged sedation, respiratory depression, coma, and death may result from the concomitant use of BUTRANS with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Drug Interactions (7)]. If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when BUTRANS is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see Drug Interactions (7), Patient Counseling Information (17)].

5.5 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of BUTRANS in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: BUTRANS-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially
decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of BUTRANS [see Warnings and Precautions (5.2)].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachetic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see Warnings and Precautions (5.2)].

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, 5.4)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.6 Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.7 QTc Prolongation
A positive-controlled study of the effects of BUTRANS in 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.

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), or other medications that prolong the QTc interval [see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.2)].

5.8 Severe Hypotension
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)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of BUTRANS. In patients with circulatory shock, BUTRANS may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of BUTRANS in patients with circulatory shock.

5.9 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury or Impaired Consciousness
In patients who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), BUTRANS may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with BUTRANS. 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
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 Risks of Use with 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 [see Patient Counseling Information (17)].

5.14 Risk of Use in 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 Risks of Use in Patients with Gastrointestinal Conditions

BUTRANS is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The buprenorphine in BUTRANS may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.16 Increased Risk of Seizures in Patients with Seizure Disorders

The buprenorphine in BUTRANS may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during BUTRANS therapy.

5.17 Risks of 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 [see Patient Counseling Information (17)].

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:

• 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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Open-Label Titration Period BUTRANS (N=1024)</th>
<th>Double-Blind Treatment Period BUTRANS (N=256)</th>
<th>Placebo (N=283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>23%</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Headache</td>
<td>9%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>8%</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>6%</td>
<td>4%</td>
<td>1%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Open-Label Titration Period BUTRANS (N=1160)</th>
<th>Open-Label Titration Period Placebo (N=219)</th>
<th>Open-Label Titration Period BUTRANS 20 (N=221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>14%</td>
<td>11%</td>
<td>6%</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>9%</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Headache</td>
<td>9%</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Application site rash</td>
<td>3%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Application site irritation</td>
<td>3%</td>
<td>8%</td>
<td>6%</td>
</tr>
</tbody>
</table>

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, pyelonephritis, and sinusitis
- Metabolism and nutrition disorders: dehydration
- Musculoskeletal and connective tissue disorders: back pain, arthralgia, pain in extremity, muscle spasms, lipodystrophy, joint swelling, neck pain, and myalgia
- Nervous system disorders: hypoesthesia, truncal, 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, angiodema, apathy, application site deratitis, asthma aggravated, bradycardia, chills, confusion, state, contact dermatitis, coordination abnormal, dehydration, depersonalization, depressed level of consciousness, depressed mood, disinhibition, disturbance in attention, diverticulitis, drug hypersensitivity, drug withdrawal syndrome, dry eye, dry skin, dysarthria, dysgeusia, dysphagia, euphoria, mood, face edema, flatulence, flushing, gait disturbance, hallucination, hiccups, hot flush, hyperglycemia, hypotension, hyperventilation, 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, rhabdomyolysis, sedation, sexual dysfunction, syncope, tachycardia, tinnitus, urinary incontinence, urinary retention, urticaria, vasodilatation, vertigo, vision blurred, visual disturbance, weight decreased, and wheezing.

6.2 Postmarketing Experience:
The following adverse reactions have been identified during post approval use of buprenorphine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
- Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
- Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- Anaphylaxis: Anaphylaxis has been reported with ingredients contained in BUTRANS. Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see Clinical Pharmacology (12.2)].

Table 5: Significant Drug Interactions with BUTRANS

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Clinical Impact:</th>
<th>Intervention:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benzodiazepines and Other Central Nervous System (CNS) Depressants</th>
<th>Clinical Impact:</th>
<th>Intervention:</th>
<th>Examples:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Due to additive pharmacologic effects, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.</td>
<td>Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see Warnings and Precautions (5.4)].</td>
<td>Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibitors of CYP3A4</th>
<th>Clinical Impact:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The concomitant use of buprenorphine and CYP3A4 inhibitors can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of BUTRANS is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the buprenorphine plasma concentration will decrease [see Clinical Pharmacology (12.3)], potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to buprenorphine.</td>
<td></td>
</tr>
</tbody>
</table>
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.3)]. Available data with BUTRANS in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction 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

<table>
<thead>
<tr>
<th>Intervention:</th>
</tr>
</thead>
<tbody>
<tr>
<td>If concomitant use is necessary, consider dosage reduction of BUTRANS until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the BUTRANS dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.</td>
</tr>
</tbody>
</table>

| Examples: |
| Macrolide antibiotics (e.g., erythromycin),azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir) |

<table>
<thead>
<tr>
<th>CYP3A4 Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Impact:</td>
</tr>
<tr>
<td>The concomitant use of buprenorphine and CYP3A4 inducers can decrease the plasma concentration of buprenorphine [see Clinical Pharmacology (12.3)], potentially resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to buprenorphine. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the buprenorphine plasma concentration will increase [see Clinical Pharmacology (12.3)], which could increase or prolong both therapeutic effects and adverse reactions and may cause serious respiratory depression.</td>
</tr>
</tbody>
</table>

| Intervention: |
| If concomitant use is necessary, consider increasing the BUTRANS dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider BUTRANS dosage reduction and monitor for signs of respiratory depression. |

| Examples: |
| Rifampin, carbamazepine, phenytoin |

<table>
<thead>
<tr>
<th>Serotonergic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Impact:</td>
</tr>
<tr>
<td>The concomitant use of opioid with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.</td>
</tr>
</tbody>
</table>

| Intervention: |
| If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue BUTRANS if serotonin syndrome is suspected. |

| Examples: |
| Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). |

<table>
<thead>
<tr>
<th>Monoamine Oxidase Inhibitors (MAOIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Impact:</td>
</tr>
<tr>
<td>MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see Warnings and Precautions (5.2)]</td>
</tr>
</tbody>
</table>

| Intervention: |
| The use of BUTRANS is not recommended for patients taking MAOIs or within 14 days of stopping such treatment. |

| Examples: |
| Phenelzine, tranylcypromine, linezolid |

<table>
<thead>
<tr>
<th>Mixed Agonist/Antagonist Opioid Analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Impact:</td>
</tr>
<tr>
<td>May reduce the analgesic effect of BUTRANS and/or precipitate withdrawal symptoms.</td>
</tr>
</tbody>
</table>

| Intervention: |
| Avoid concomitant use. |

| Examples: |
| Butorphanol, nalbuphine, pentazocine |

<table>
<thead>
<tr>
<th>Muscle Relaxants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Impact:</td>
</tr>
<tr>
<td>Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.</td>
</tr>
</tbody>
</table>

| Intervention: |
| Monitor patients receiving muscle relaxants and BUTRANS for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of BUTRANS and/or the muscle relaxant as necessary. |

<table>
<thead>
<tr>
<th>Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Impact:</td>
</tr>
<tr>
<td>Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.</td>
</tr>
</tbody>
</table>

| Intervention: |
| Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed. |

<table>
<thead>
<tr>
<th>Anticholinergic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Impact:</td>
</tr>
<tr>
<td>The concomitant use of opioid analgesics, including buprenorphine, and anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.</td>
</tr>
</tbody>
</table>

| Intervention: |
| Monitor patients for signs of urinary retention or reduced gastric motility when BUTRANS is used concomitantly with anticholinergic drugs. |
times that of human subjects who received one BUTRANS 20 mcg/hour, the maximum recommended human dose (MRHD) [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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. 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.3)].

Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. An opioid antagonist such as naloxone must be available for reversal of opioid-induced respiratory depression in the neonate. BUTRANS is not recommended for use in women immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including BUTRANS, 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.

Data

Animal Data

Studies in rats and rabbits demonstrated no evidence of teratogenicity following BUTRANS or subcutaneous (SC) administration of buprenorphine during the period of 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 to 17). Rabbits were administered four BUTRANS 20 mcg/hour every 3 days (Gestation Days 6, 9, 12, 15, 18, and 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.

In a pre- 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 Lactation

Risk Summary

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with BUTRANS.

Clinical Considerations

Monitor infants exposed to BUTRANS through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of buprenorphine is stopped or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2), Preclinical Pharmacology (12.2), Nonclinical Toxicology (13.1)].

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)]. Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of BUTRANS slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see Warnings and Precautions (5.5)].

8.6 Hepatic Impairment

In a study utilizing intravenous buprenorphine, peak plasma levels (Cmax) 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 for 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.
by state and federal 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 limit 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)]. 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 chewing, swallowing, snorting, or injecting buprenorphine extracted from the transdermal system.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

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 dosage 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 (e.g., 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 (2.4)]. If BUTRANS is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lachrymation, rhinorrea, 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 signs [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, and, in some cases, pulmonary edema, 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 [see Clinical Pharmacology (12.2)].

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 syndrome. The severity of the withdrawal symptoms experienced 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, 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)-a-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-a-methyl]-[5a, 7a, (S)]. The structural formula is:

![Buprenorphine structural formula]

The molecular weight of buprenorphine is 467.6; the empirical formula is C29H41NO4. 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
Five different strengths of BUTRANS are available: 5, 7.5, 10, 15, and 20 mcg/hour (Table 6). The proportion of buprenorphine mixed in the adhesive matrix is the same in each of the five 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>
<thead>
<tr>
<th>BUTRANS Product Specifications</th>
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<tbody>
<tr>
<td><strong>Buprenorphine</strong></td>
</tr>
<tr>
<td><strong>Delivery Rate (mcg/hour)</strong></td>
</tr>
<tr>
<td>BUTRANS 5</td>
</tr>
<tr>
<td>BUTRANS 7.5</td>
</tr>
<tr>
<td>BUTRANS 10</td>
</tr>
<tr>
<td>BUTRANS 15</td>
</tr>
<tr>
<td>BUTRANS 20</td>
</tr>
</tbody>
</table>

BUTRANS is a rectangular or square, beige-colored system consisting of a protective liner and functional layers. Proceeding from the outer surface toward the skin 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.

12.1 Mechanism of Action
Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the 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
Buprenorphine produces respiratory depression by direct action on brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brainstem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Buprenorphine causes miosis, even in total darkness. 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 overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
Buprenorphine causes a reduction in motility associated with an increase in smooth muscle 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, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Buprenorphine produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

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 (5.8)]. 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 adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see Adverse Reactions (6.2)]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal
hormone levels have not been adequately controlled for in studies conducted to date [see Adverse Reactions (6.2)].

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

Concentration–Efficacy Relationships
The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of buprenorphine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [see Dosage and Administration (2.1, 2.3)].

Concentration–Adverse Reaction Relationships
There is a relationship between increasing buprenorphine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see Dosage and Administration (2.1, 2.2, 2.3)].

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 7. Plasma buprenorphine concentrations after titration showed no further change over the 60-day period studied.

Table 7: Pharmacokinetic Parameters of BUTRANS in Healthy Subjects, Mean (%CV)

<table>
<thead>
<tr>
<th>Single 7-day Application</th>
<th>AUCinf (pg.h/mL)</th>
<th>Cmax (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUTRANS 5 mcg/hour</td>
<td>12087 (37)</td>
<td>176 (67)</td>
</tr>
<tr>
<td>BUTRANS 10 mcg/hour</td>
<td>27035 (29)</td>
<td>191 (34)</td>
</tr>
<tr>
<td>BUTRANS 20 mcg/hour</td>
<td>54294 (36)</td>
<td>471 (49)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple 7-day Applications</th>
<th>AUCinf (pg.h/mL)</th>
<th>Cmax (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUTRANS 10 mcg/hour, steady-state</td>
<td>27543 (33)</td>
<td>224 (35)</td>
</tr>
</tbody>
</table>

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 (2.6)]. 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 (2.6)].

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 drug absorption 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 adjust-
The total clearance of buprenorphine is approximately 55 L/hour in postoperative patients.

**Drug Interaction Studies**

**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)].

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. Cmax and AUC for buprenorphine increased by up to 1.6 and 1.9 fold, and Cmax 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)].

**Effect of CYP3A4 Inducers**

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

**Specific Populations**

**Age: 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 Cmax or AUC [see Use in Specific Populations (8.5)].

**Sex**

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

**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 metabolism 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, Warnings and Precautions (5.10), and Use in Specific Populations (8.6)].

**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.

**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 three in vitro genetic toxicity 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 BUTRANS 10 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. Seventy 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.

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.

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 patients randomized to BUTRANS, 9% discontinued due to lack of efficacy and 16% due to adverse events. 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 Transdermal System is supplied in cartons containing 4 individually-packaged systems and a pouch containing 4 Patch-Disposal Units.
BUTRANS (buprenorphine) 5 mcg/hour Transdermal Systems are square, beige-colored adhesive patches measuring 45 mm by 45 mm. Each system is printed in blue with the BUTRANS logo and 5 mcg/hr and are supplied in a 4-count carton [NDC 59011-750-04].

BUTRANS (buprenorphine) 7.5 mcg/hour Transdermal Systems are rectangular, beige-colored adhesive patches measuring 58 mm by 45 mm. Each system is printed in blue with the BUTRANS logo and 7.5 mcg/hr and are supplied in a 4-count carton [NDC 59011-757-04].

BUTRANS (buprenorphine) 10 mcg/hour Transdermal Systems are rectangular, beige-colored adhesive patches measuring 68 mm by 45 mm. Each system is printed in blue with the BUTRANS logo and 10 mcg/hr and are supplied in a 4-count carton [NDC 59011-758-04].

BUTRANS (buprenorphine) 15 mcg/hour Transdermal Systems are square, beige-colored adhesive patches measuring 72 mm by 59 mm. Each system is printed in blue with the BUTRANS logo and 15 mcg/hr and are supplied in a 4-count carton [NDC 59011-759-04].

BUTRANS (buprenorphine) 20 mcg/hour Transdermal Systems are square, beige-colored adhesive patches measuring 72 mm by 72 mm. Each system is printed in blue with the BUTRANS logo and 20mcg/hr and are supplied in a 4-count carton [NDC 59011-760-04].

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

17 PATIENT COUNSELING INFORMATION
Advises 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 dosage is increased, and that it can occur even at recommended doses [see Warnings and Precautions (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 [see Dosage and Administration (2.7)].

Interaction with Benzodiazepines and Other CNS Depressants Inform patients and caregivers that potentially fatal additive effects may occur if BUTRANS is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [see Warnings and Precautions (5.4)].

Adrenal Insufficiency Inform patients that BUTRANS may cause or worsen symptoms of adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see Warnings and Precautions (5.6)].

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 [see Dosage and Administration (2.6)].

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 [see Dosage and Administration (2.6)].

3. To avoid exposing the BUTRANS application site to external heat sources, hot water, or prolonged direct sunlight [see Warnings and Precautions (5.13)].

4. Do not discontinue BUTRANS without first discussing the need for a tapering regimen with the prescriber [see Dosage and Administration (2.3)].

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) [see Warnings and Precautions (5.8)].

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 [see Warnings and Precautions (5.12), Contraindications (4), Adverse Reactions (6)].

Pregnancy
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)], Use in Specific Populations (8.1), Embryofetal Toxicity Inform female patients of reproductive potential that BUTRANS can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations (8.1)].
Lactation
Advise patients that breastfeeding is not recommended during treatment with BUTRANS [see Use in Specific Populations (8.2)]

Infertility
Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [Use in Specific Populations (8.3)].

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 [see Warnings and Precautions (5.17)].

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see Adverse Reactions (6), Clinical Pharmacology (12.2)].

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 them 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 [see Dosage and Administration (2.7)].

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 Therapy Systems Corp., West Caldwell, NJ 07006

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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.
- Taking BUTRANS with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your BUTRANS. They could die from taking it. Store BUTRANS away from children and in a safe place to prevent stealing or abuse. Selling or giving away BUTRANS is against the law.

Do not use BUTRANS if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before applying BUTRANS, tell your healthcare provider if you have a history of:
- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating

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. Not recommended during treatment with BUTRANS. It 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. Use the lowest effective dose for the shortest time needed.
- 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 feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

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: 12/2016
Instructions for Use

**BUTRANS® (BYOO-trans)**
(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 A). These 4 sites (located on both sides of the body) provide 8 possible BUTRANS application sites.
- You should change the skin site where you apply BUTRANS each week, making sure that at least 3 weeks (21 days) pass before you re-use the same skin site.
- 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.

**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
- 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.

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

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

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

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

Always remove the leftover patches from their protective pouch and remove the protective liner. 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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