WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING BREATHING PROBLEMS; ACCIDENTAL EXPOSURE; and WITHDRAWAL SYNDROME IN NEWBORNS; and RISKS FROM USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse
Butrans is a long-acting (extended-release) opioid pain medicine that can put you and other users at risk for overdose and death. Even if you use your dose correctly as prescribed, you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Life-Threatening Breathing Problems
When you first start using Butrans, or when your dose is increased, serious or life-threatening breathing problems that can lead to death may occur, and may occur even at recommended doses during the normal course of therapy. Do not chew, swallow, snort, or inject buprenorphine from the patch because this can lead to overdose and death.

Accidental Exposure
Accidental exposure, especially in children, may result in breathing problems, overdose, or death.

Withdrawal Syndrome in Newborns
Prolonged use of Butrans when you are pregnant can cause withdrawal symptoms in your newborn baby that may be life-threatening if not recognized and treated.

Use with Benzodiazepines or Other CNS Depressants
Use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, can result in severe drowsiness, breathing problems, coma and death.

Please read accompanying Brief Summary and Full Prescribing Information, including Boxed Warning, Medication Guide, and Instructions for Use.
For more information, please consult with your healthcare professional or visit Butrans.com.
Welcome to Butrans

Your healthcare professional has prescribed you Butrans (BYOO-trans) to help relieve the chronic pain that you have been experiencing. This guide will provide you with helpful information about what to expect as you get started on Butrans. Remember to keep this guide in a handy place and refer to it as needed.

If you have any questions or want more details about your treatment with Butrans, be sure to:

- Contact the healthcare professional who prescribed Butrans for you, or the pharmacist who filled the prescription
- Refer to the enclosed Butrans Brief Summary, Medication Guide, and Instructions for Use
- Visit Butrans.com, where you will find helpful information and resources

What is Butrans?

Butrans is a strong prescription pain medicine that contains an opioid (narcotic). It 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 (e.g., acetaminophen, ibuprofen, or celecoxib) or immediate-release opioid medicines, do not treat your pain well enough, you experience side effects when taking them, or they are deemed otherwise inadequate.

Butrans is only used to treat pain that continues around-the-clock (pain that is constant).
What you should know about Butrans

Butrans is a long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you use your dose correctly as prescribed, you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Do not use Butrans if you:

- Have severe asthma, trouble breathing, or other lung problems
- Have a bowel blockage or have narrowing of the stomach or intestines
- Are allergic to buprenorphine

Each Butrans patch should be worn continuously for 7 days. The medicine in a Butrans patch is absorbed through the skin, and is delivered continuously for 7 days.

Butrans is available in 5 different strengths: 5, 7.5, 10, 15, and 20 mcg/hour patches. These different strengths give your healthcare professional options for finding the right level of medication to help treat your chronic pain.

Before applying Butrans, tell your healthcare professional if you have a history of head injury or seizures; problems breathing or urinating; liver, kidney, thyroid, pancreas, or gallbladder problems; heart rhythm abnormalities (Long QT Syndrome); abuse of street or prescription drugs; alcohol addiction; or mental health problems.

Please see pages 10 and 11 for Additional Important Safety Information for Butrans.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please read accompanying Brief Summary and Full Prescribing Information, including Boxed Warning, Medication Guide, and Instructions for Use.
What to expect when starting treatment

The first time you apply Butrans, or at any dosage increase, it can take up to 3 days for your body to absorb enough of the medicine in the patch for Butrans to reach steady levels in your body. If you think you are not getting enough pain relief or if your pain increases during this period, contact your healthcare professional. **Do not change your dose unless directed by your healthcare professional.**

Patch application site tracker

It’s important to change the skin site where you apply the patch each week, making sure that at least 3 weeks (21 days) pass before you re-use the same skin site. The tracker below is designed to help you keep track of your application sites and other important details regarding your Butrans treatment:

- The date you apply a patch
- The date you remove it
- How you disposed of it [by folding and flushing it (FF) it or by using the Patch-Disposal Unit (PDU)]
- Where you applied the patch, and on which side of your body (left or right)

<table>
<thead>
<tr>
<th>Week</th>
<th>Date applied</th>
<th>Date removed</th>
<th>Disposal (FF/PDU)</th>
<th>Upper outer arm (L/R)</th>
<th>Upper back (L/R)</th>
<th>Upper chest (L/R)</th>
<th>Side of chest (L/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAMPLE</strong></td>
<td>10/15/16</td>
<td>10/22/16</td>
<td>PDU</td>
<td>Right</td>
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<td>Week 1</td>
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Please see pages 6-9 for additional information on the application and disposal of Butrans.

Please read accompanying Brief Summary and Full Prescribing Information, including Boxed Warning, Medication Guide, and Instructions for Use.
Continuing treatment with Butrans

Communicate
As you continue on your Butrans treatment, it is important that you communicate with your healthcare professional and let him or her know how your treatment is going, especially as you get started. Follow-up visits are a great time to have these discussions.

Be patient
Let your healthcare professional know if you think that you are not getting enough pain relief or if you experience pain flare-ups. Your healthcare professional may decide to increase your Butrans dose, or prescribe you an additional pain medication to take. Your healthcare professional will make this decision after waiting at least 72 hours. It is important to remember that it can take up to 3 days for your new Butrans patch to reach steady levels in your body.

Speak up
Be sure to let your healthcare professional know if you experience any side effects with your Butrans therapy. Do not stop taking Butrans until you talk to your healthcare professional. Your healthcare professional may decide to decrease your Butrans dose in an effort to minimize unwanted side effects.

Working together with your healthcare professional
You and your healthcare professional should discuss the goals for your Butrans therapy and talk about finding a dosage strength that provides a balance of pain relief and side effects. Work with your healthcare professional to periodically reassess the continued need for Butrans.
Applying Butrans

Butrans patches are available in different strengths and patch sizes. Make sure you have the right strength patch that has been prescribed for you, and review the steps below before applying your Butrans patch.

The application instructions provided here are intended as a guide, and do not include all of the steps you must follow when using Butrans. Please review the Instructions for Use you received with your Butrans prescription before starting your treatment with Butrans. If you have any questions, talk to your healthcare professional or pharmacist.

1 Choose an application site
- Butrans should be applied to the left or right upper outer arm, upper chest, upper back, or the side of the chest for a total of 8 different application sites in all

Choose an application site
- It is important to change the skin site where you apply your Butrans patch every week (exactly 7 days), making sure that at least 3 weeks (21 days) pass before you re-use the same site
- If you are wearing a patch, remember to remove it before applying a new one
- Do not use soap, alcohol, lotions, oils, or other products to remove any leftover adhesive from a patch, because this may cause more medicine to pass through the skin
- Do not apply more than 1 patch at the same time unless your healthcare professional tells you to do so
- If you are using 2 patches as prescribed, remember to apply them at the same site right next to each other. Always apply and remove the 2 patches together at the same time

2 Prepare the skin
- Butrans should be applied to hairless or nearly hairless skin. If needed, you can clip the hair at the site, but do not shave the area
- The skin should be free of cuts and irritation (rashes, swelling, redness, or other skin problems)
- Use only water to clean the site, and allow the skin to dry completely before applying the patch (do NOT use soaps, alcohol, oils, lotions, or abrasive devices)
Remove the patch from its pouch
- Each patch is sealed in its own protective pouch
- Do not use a patch if the seal on its protective pouch is broken or if the patch is cut, damaged, or changed in any way
- Cut the pouch open along the dotted line and remove the patch
- Do not remove the patch from the pouch until you are ready to use it

Remove the liner from the patch
- Hold the patch with its protective liner facing you
- Gently bend the patch along the faint line and peel back the larger portion of the liner, which covers the sticky surface of the patch
- Do not touch the sticky side of the patch with your fingers

Place the patch on your skin
- Using the smaller part of the protective liner as a handle, apply the sticky side of the patch to one of the 8 body locations described on page 6

Remove the protective liner
- While 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

Please read accompanying Brief Summary and Full Prescribing Information, including Boxed Warning, Medication Guide, and Instructions for Use.
Applying Butrans (continued)

7 Press the patch firmly into place

- Press down on the entire patch for about 15 seconds with the palm of your hand (do not rub)
- Make sure the patch firmly sticks to the skin and go over the edges with your finger to ensure good contact around the patch

8 Wash up

- Always wash your hands after applying or handling a Butrans patch

How to dispose of Butrans

1 Use the Patch-Disposal Unit you received with your prescription

- Peel back the disposal unit liner to show the sticky surface
- Place the sticky side of the used or unused patch to the indicated area on the disposal unit
- Close the disposal unit by folding the sticky sides together. Press firmly and smoothly over the entire disposal unit so that patch is sealed within
- The closed disposal unit, with the patch sealed inside, may be thrown away in the trash
- **Use one Patch-Disposal Unit for each patch**
- **Do not put used or unused patches in household trash without first sealing them in the Patch-Disposal Unit**

2 Fold and flush

- Fold the sticky sides of the used or unused patch together, then flush it down the toilet right away
- **Do not flush the pouch or the protective liner down the toilet. These can be put in the trash**

Please read accompanying Brief Summary and Full Prescribing Information, including Boxed Warning, Medication Guide, and Instructions for Use.
What if the patch starts to loosen?

• Apply first aid tape only to the edges of the patch
• If the patch is still not sticking, cover it carefully and completely with special see-through adhesive dressing (e.g., 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. Your healthcare professional or pharmacist will advise what kind of dressing should be used

What if the patch falls off?

• If your patch falls off right after applying, throw it away and put a new one on at a different skin site (see page 8 for disposal instructions)
• If your patch falls off later, but before 7 days of use, throw it away and put a new one on at a different skin site. Let your healthcare professional know that this has happened. Do not replace the new patch until 7 days have passed (or as directed by your healthcare professional)
• Do not touch the sticky side of the patch with your fingers. Patches that fall off should not be re-applied
WARNINGS

• Use of Butrans, even when used as recommended, can result in addiction, abuse and misuse, which could lead to overdose and death

• Get emergency help right away if you take too much Butrans (overdose)

• The risk of serious or life-threatening breathing problems that could lead to death can occur even at recommended doses. The risk is greatest when you first start using Butrans or when your dose is increased. Patients who have lung disease or are elderly, frail, or in poor general health are at increased risk, especially if Butrans is given with other drugs that cause breathing problems. Seek medical attention immediately if you have trouble breathing

• 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. Do not use these together unless you are directed to do so by your healthcare provider

• Never give anyone else your Butrans. They could die from using it. Store Butrans away from children and in a safe place to help prevent abuse or theft. Selling or giving away Butrans is against the law

• Accidental exposure, especially by a child, may result in breathing problems, overdose, or death. Be sure to store Butrans safely and to dispose of unused patches when Butrans is no longer needed; use the Patch-Disposal Unit or fold the patch in half and flush it down the toilet (see the detailed Instructions for Use provided with the Butrans patch)

• Tell your healthcare provider if you are pregnant or planning to become pregnant.

Prolonged use of Butrans while you are pregnant can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated

• Tell your healthcare provider if you are breast-feeding. Breast-feeding is not recommended during treatment with Butrans. It may harm your baby

• Tell your healthcare provider about any prescription or over-the-counter medicines, vitamins, or herbal supplements you are taking. Using Butrans with certain other medicines can cause serious side effects that could lead to death

• When using Butrans, do not 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

• Butrans could cause adrenal insufficiency, a potentially life-threatening condition which may cause symptoms of nausea, vomiting, anorexia, fatigue, weakness, dizziness and low blood pressure. Seek medical attention if you experience these symptoms

Please read accompanying Brief Summary and Full Prescribing Information, including Boxed Warning, Medication Guide, and Instructions for Use.
WARNINGS (continued)

- Butrans may cause symptoms of low blood pressure such as dizziness, lightheadedness, or fainting. If you experience these symptoms, you should sit or lie down and be careful when you get up from a sitting or lying position
- Butrans may complicate head injuries. Butrans should not be used by those with disturbances in consciousness or coma
- **Do not stop using Butrans without talking to your healthcare provider**
  - Tell your healthcare provider if you develop a fever. While using Butrans, do NOT expose Butrans or the skin near where Butrans is applied to hot water or prolonged direct sunlight; avoid sunbathing, taking hot baths, hot tubs, saunas, heating pads, electric blankets, heated waterbeds, and heat or tanning lamps. These activities can increase the amount of medicine your Butrans delivers and cause an overdose that can lead to death
  - 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
  - Butrans may increase the frequency of seizures in patients who experience seizures and may increase the risk of seizures in other settings associated with seizures. Tell your healthcare provider if you have a history of seizures
  - When using Butrans, do not drive or operate heavy machinery until you know how Butrans affects you. Butrans can make you sleepy, dizzy, or lightheaded, and may reduce your mental and physical ability to perform these activities safely

SIDE EFFECTS

- The most common side effects reported by patients treated with Butrans in the clinical trials were nausea, headache, application site itch, dizziness, constipation, sleepiness, vomiting, application site redness, dry mouth, and application site rash. Call your healthcare provider if you have any of these symptoms and they are severe
- These are not all the possible side effects of Butrans. Call your doctor for medical advice about side effects

Please read accompanying Brief Summary and Full Prescribing Information, including Boxed Warning, Medication Guide, and Instructions for Use.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING BREATHING PROBLEMS; ACCIDENTAL EXPOSURE; and WITHDRAWAL SYNDROME IN NEWBORNS; and RISKS FROM USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse
Butrans is a long-acting (extended-release) opioid pain medicine that can put you and other users at risk for overdose and death. Even if you use your dose correctly as prescribed, you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Life-Threatening Breathing Problems
When you first start using Butrans, or when your dose is increased, serious or life-threatening breathing problems that can lead to death may occur, and may occur even at recommended doses during the normal course of therapy. Do not chew, swallow, snort, or inject buprenorphine from the patch because this can lead to overdose and death.

Accidental Exposure
Accidental exposure, especially in children, may result in breathing problems, overdose, or death.

Withdrawal Syndrome in Newborns
Prolonged use of Butrans when you are pregnant can cause withdrawal symptoms in your newborn baby that may be life-threatening if not recognized and treated.

Use with Benzodiazepines or Other CNS Depressants
Use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, can result in severe drowsiness, breathing problems, coma and death.

For more information, please visit Butrans.com
Please read accompanying Brief Summary and Full Prescribing Information, including Boxed Warning, Medication Guide, and Instructions for Use.
For more information, please consult with your healthcare professional or visit Butrans.com.

To report SUSPECTED SIDE EFFECTS, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or www.fda.gov/safety/medwatch.
SUMMARY OF INFORMATION ABOUT BUTRANS
The information below does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING BREATHING PROBLEMS; ACCIDENTAL EXPOSURE; and WITHDRAWAL SYNDROME IN NEWBORNS; and RISKS FROM USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

**Addiction, Abuse, and Misuse**
Butrans® (buprenorphine) is a long-acting (extended-release) opioid pain medicine that can put you and other users at risk for overdose and death. Even if you use your dose correctly as prescribed, you are at risk for opioid addiction, abuse, and misuse that can lead to death.

**Life-Threatening Breathing Problems**
When you first start using BUTRANS, or when your dose is increased, serious or life-threatening breathing problems that can lead to death may occur, and may occur even at recommended doses during the normal course of therapy. Do not chew, swallow, snort, or inject buprenorphine from the patch because this can lead to overdose and death.

**Accidental Exposure**
Accidental exposure, especially in children, may result in breathing problems, overdose, or death.

**Withdrawal Syndrome in Newborns**
Prolonged use of BUTRANS when you are pregnant can cause withdrawal symptoms in your newborn baby that may be life-threatening if not recognized and treated.

**Use with Benzodiazepines or Other CNS Depressants**
Use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, can result in severe drowsiness, breathing problems, coma and death.

**What is Butrans?**
- Butrans® (buprenorphine) Transdermal System is a strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain that is severe enough to require daily, around-the-clock, long-term treatment with an opioid, when other pain treatments such as nonopioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them
- Butrans is a long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you use Butrans correctly as prescribed, you are at risk for opioid addiction, abuse, and misuse that can lead to death
- Butrans is only used to treat pain that continues around-the-clock (pain that is constant)
- Butrans is for use on intact and non-irritated skin only. Each Butrans patch should be worn continuously for 7 days

**Who should not use Butrans?**
- People who have any of these medical conditions should NOT use Butrans:
  - Severe asthma, trouble breathing, or other lung problems
  - A bowel blockage or narrowing of the stomach or intestines
  - Allergies to buprenorphine (the opioid in Butrans)
- Butrans should not be used in patients younger than 18 years of age
What warnings should I know before using Butrans?

- Use of Butrans, even when used as recommended, can result in addiction, abuse, and misuse, which could lead to overdose and death
- Using Butrans in any way other than how it is prescribed, including chewing or swallowing it or putting it in the mouth, may lead to choking, overdose, or death
- Using Butrans without a prescription is against the law and may lead to criminal charges. Opioid medications such as Butrans are sought by people who abuse drugs or have problems with addiction. Store Butrans in a safe place to help prevent abuse
- Never give anyone else your Butrans. They could die from using it. Store Butrans away from children and in a safe place to help prevent abuse or theft. Selling or giving away Butrans is against the law
- The risk of serious or life-threatening breathing problems that could lead to death can occur even at recommended doses. The risk is greatest when you first start using Butrans or when your dose is increased. Patients who have lung disease or are elderly, frail, or in poor general health are at increased risk, especially if Butrans is given with other drugs that cause breathing problems
- If you experience breathing problems caused by Butrans and are not treated right away, you could stop breathing and die. Get emergency help right away if you have trouble breathing or use too much Butrans (overdose)
- Accidental exposure, especially in a child, may result in breathing problems, overdose, or death
- Be sure to store Butrans safely and to dispose of unused patches when Butrans is no longer needed; use the Patch-Disposal Unit, or fold the patch in half and flush it down the toilet (see the detailed Instructions for Use provided with the Butrans patch)
- Using Butrans with other opioid medicines, benzodiazepines, alcohol or other central nervous system depressants, such as sleeping pills, medicines for anxiety, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, or street drugs may cause severe drowsiness, decreased awareness, low blood pressure, breathing problems, coma, and death. Do not use these types of medicines together unless you are directed to do so by your healthcare provider
- Butrans could cause adrenal insufficiency, a potentially life-threatening condition which may cause symptoms of nausea, vomiting, anorexia, fatigue, weakness, dizziness and low blood pressure. Seek medical attention if you experience these symptoms
- Butrans should be avoided if you have a history of Long QT Syndrome or an immediate family member with this condition, or if you are taking certain medicines for heart rhythm abnormalities
- Butrans may cause symptoms of low blood pressure, such as dizziness, lightheadedness, or fainting. If you experience these symptoms, you should sit or lie down and be careful when you get up from a sitting or lying position
- Butrans may complicate head injuries. Butrans should not be used by those with disturbances in consciousness or coma
- In rare cases, burns or blisters may develop on the skin where Butrans has been applied. This can happen soon after you start using Butrans, or after you have already been using it for a while. If your skin develops burns or blisters where you’ve applied Butrans, contact your healthcare provider right away; he or she may instruct you to discontinue Butrans
- Some people are, or may become, sensitive or allergic to buprenorphine (the opioid in Butrans) while using Butrans. This may lead to itching, swelling, and rashes or hives on the skin; in some cases, reactions including swelling of the lips, tongue, roof of mouth, throat, or windpipe may occur, making it difficult to swallow or breathe

What should I tell my healthcare provider?

- Tell your healthcare provider if you are pregnant or planning to become pregnant. Prolonged use of Butrans while you are pregnant can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. Butrans can cause fetal harm. Chronic use of opioids may cause reduced fertility
- Tell your healthcare provider if you are breastfeeding. Breastfeeding is not recommended during treatment with Butrans. It may harm your baby
- The amount of buprenorphine a baby might receive from breastfeeding depends on the dose of Butrans the mother is using, how much milk the baby consumes, and how the mother’s body processes Butrans. Breast-fed babies may experience withdrawal symptoms when their mothers stop using Butrans
- Tell your healthcare provider about any prescription or over-the-counter medicines, vitamins, or herbal supplements you are taking. Using Butrans with certain other medicines can cause serious side effects
- Tell your healthcare provider if you have or have had a head injury or seizure; problems breathing or urinating; an intestinal blockage; liver, kidney, thyroid, pancreas, or gallbladder problems; heart rhythm abnormalities (Long QT Syndrome); abuse of street or prescription drugs, alcohol addiction, or mental health problems
- Tell your healthcare provider if you develop a fever

What if I use too much Butrans?

- Get emergency help right away if you use too much Butrans. Using too much Butrans can result in an overdose, and can cause serious or life-threatening breathing problems that can lead to death

What side effects might I have while taking Butrans?

- The most common side effects reported by patients treated with Butrans in the clinical trials were nausea, headache, application site itch, dizziness, constipation, sleepiness, vomiting, application site redness, dry mouth, and application site rash. Call your healthcare provider if you have any of these symptoms and they are severe
- The most common serious side effects occurring during clinical trials with Butrans included chest pain, abdominal pain, vomiting, dehydration, and increased blood pressure
- 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 the FDA at 1-800-FDA-1088. For more information, go to dailymed.nlm.nih.gov
What other medicines might interact with Butrans?

- Using Butrans with other opioid medicines, benzodiazepines, alcohol or other central nervous system depressants, such as sleeping pills, medicines for anxiety, tranquilizers, muscle relaxants, general anesthetics, antipsychotics or street drugs may cause severe drowsiness, decreased awareness, low blood pressure, breathing problems, coma, and death. Do not use these types of medicines together unless you are directed to do so by your healthcare provider.

- It is extremely dangerous to self-administer benzodiazepines while using Butrans. Do not use these types of drugs unless you are told to do so by your healthcare provider.

- When using Butrans, do not 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.

- Some medicines (cytochrome P450 3A4 inhibitors including antibiotics such as erythromycin, anti-fungal medicines such as ketoconazole, and medicines for HIV such as ritonavir) can increase the amount of buprenorphine (the opioid in Butrans) in your blood if you take them while using Butrans. This may lead to breathing problems and extreme drowsiness. Tell your healthcare provider if you are taking these types of medicines before using Butrans.

- If you stop taking certain other medicines (cytochrome P450 3A4 inducers, including carbamazepine, phenytoin, and rifampin) while you are using Butrans, this may increase the amount of buprenorphine (the opioid in Butrans) in your blood and may cause adverse effects and serious breathing problems. Tell your healthcare provider before you stop taking any other medicines you have been taking regularly while using Butrans.

- Opioids could cause a rare but potentially life-threatening condition resulting from use with serotonergic drugs (e.g. 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). Tell your healthcare provider if you are taking or plan to take serotonergic drugs.

- Avoid using Butrans while using any drugs that inhibit monoamine oxidase including phenelzine, tranylcypromine, linezolid.

- Avoid using Butrans with mixed agonist/antagonist opioid analgesics including butorphanol, nalbuphine and pentazocine.

- The use of buprenorphine (the opioid in Butrans) with muscle relaxants may cause increased breathing problems.

- Opioids can reduce the efficacy of diuretics.

- The use of buprenorphine (the opioid in Butrans) with anticholinergic drugs may cause urinary retention and/or severe constipation which may lead to bowel blockage.

The risk information provided here is not comprehensive. To learn more, talk with your healthcare provider or pharmacist. The FDA-approved product labeling can be found at Purduepharma.com/ButransPI or 1-888-726-7535.

Distributed by: Purdue Pharma L.P., Stamford, CT 06901-3431
www.purduepharma.com or call 1-888-726-7535
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

---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, 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)

-DOSEAGE 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)

DOSAGE FORMS AND STRENGTHS
Transdermal system: 5 mcg/hour, 7.5 mcg/hour, 10 mcg/hour, 15 mcg/hour, and 20 mcg/hour. (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)

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

---DRUG INTERACTIONS---

- 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)

---USE IN SPECIFIC POPULATIONS---

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended (8.2).
- Hepatic Impairment: Consider use of an alternate analgesic that may permit more flexibility in dosing. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
Revised: 12/2016
**Full Prescribing Information**

**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 for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

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

**2 DOSAGE AND ADMINISTRATION**

**2.1 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)].

- 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)].

- 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 to not 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.

**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>
Conversion from Methadone to BUTRANS

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

2.3 Titration and Maintenance of Therapy

Individually titrate BUTRANS to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving BUTRANS to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see Warnings and Precautions (5.1)]. Frequent communication is important among the prescriber, other members of healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

The minimum BUTRANS titration interval is 72 hours, based on the pharmacokinetic profile and time to reach steady state levels [see Clinical Pharmacology (12.3)]. The maximum BUTRANS dose is 20 mcg/hour. Do not exceed a dose of one 20 mcg/hour BUTRANS system due to the risk of QTc interval prolongation. In a clinical trial, BUTRANS 40 mcg/hour (given as two BUTRANS 20 mcg/hour systems) resulted in prolongation of the QTc interval [see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)].

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

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 reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate 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 patients with severe hepatic impairment. As BUTRANS is only intended for 7-day application, consider use of an alternate analgesic that may permit more flexibility with the dosing in patients with severe hepatic impairment [see Warnings and Precautions (5.11), 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 BUTRANS to the upper outer arm, upper chest, upper back or the side of the chest. These 4 sites (each present on both sides of the body) provide 8 possible application sites. Rotate BUTRANS among the 8 described skin sites. After BUTRANS removal, wait a minimum of 21 days before reapplying to the same skin site [see Clinical Pharmacology (12.3)].
- Apply BUTRANS to a hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped, not shaven. Do not apply BUTRANS to irritated skin. If the application site must be cleaned, clean the site with water only. Do not use soaps, alcohol, oils, lotions, or abrasive devices. Allow the skin to dry before applying BUTRANS.
- Incidental exposure of the BUTRANS patch to water, such as while bathing or showering is acceptable based on experience during clinical studies.
- If problems with adhesion of BUTRANS occur, the edges may be taped with first aid tape. If problems with lack of adhesion continue, the patch may be covered with waterproof or semipermeable adhesive dressings suitable for 7 days of wear.

- If BUTRANS falls off during the 7-day dosing interval, dispose of the transdermal system properly and place a new BUTRANS patch on at a different skin site.
- When changing the system, instruct patients to remove BUTRANS and dispose of it properly [see Dosage and Administration (2.7)].
- 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 remaining from a prescription as soon as they are no longer needed.

3 DOSAGE FORMS AND STRENGTHS

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

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.

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, cachectic, 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 on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a BUTRANS dose of 10 mcg/hour; however, a BUTRANS dose of 40 mcg/hour (given as two BUTRANS 20 mcg/hour Transdermal Systems) was observed to prolong the QTc interval. 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
Advising 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:

- Addiction, Abuse, and Misuse [see Warnings and Precautions (5.1)]
- Life-Threatening Respiratory Depression [see Warnings and Precautions (5.2)]
- Neonatal Opioid Withdrawal Syndrome [see Warnings and Precautions (5.3)]
- Interactions with Benzodiazepines or Other CNS Depressants [see Warnings and Precautions (5.4)]
- Adrenal Insufficiency [see Warnings and Precautions (5.5)]
- QTc Prolongation [see Warnings and Precautions (5.6)]
- Severe Hypotension [see Warnings and Precautions (5.7)]
- Hepatotoxicity [see Warnings and Precautions (5.8)]
- Application Site Skin Reactions [see Warnings and Precautions (5.11)]
- Anaphylactic/Allergic Reactions [see Warnings and Precautions (5.12)]
- Gastrointestinal Effects [see Warnings and Precautions (5.13)]
- Seizures [see Warnings and Precautions (5.15)]

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-Naive Patients

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>MedDRA</th>
<th>BUTRANS 10</th>
<th>BUTRANS 20</th>
<th>BUTRANS 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>23%</td>
<td>13%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>10%</td>
<td>4%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9%</td>
<td>5%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>8%</td>
<td>4%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>8%</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>7%</td>
<td>4%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>6%</td>
<td>4%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>9%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Application site rash</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>6%</td>
<td>4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>7%</td>
<td>4%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>6%</td>
<td>4%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6%</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

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>MedDRA</th>
<th>BUTRANS 10</th>
<th>BUTRANS 20</th>
<th>BUTRANS 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>14%</td>
<td>11%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>9%</td>
<td>13%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9%</td>
<td>8%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>6%</td>
<td>4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>5%</td>
<td>4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>6%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Application site erythema</td>
<td>3%</td>
<td>10%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Application site rash</td>
<td>3%</td>
<td>8%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Application site irritation</td>
<td>2%</td>
<td>6%</td>
<td>2%</td>
<td></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 4: Adverse Reactions Reported in Titration-to-Effect Placebo/Active-Controlled Clinical Trials with Incidence ≥ 2%

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>BUTRANS (N=392)</th>
<th>Placebo (N = 261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>21%</td>
<td>6%</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Application site erythema</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Application site rash</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Application site irritation</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Stomach discomfort</td>
<td>2%</td>
<td>0%</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, nasopharyngitis, influenza, sinusitis, and upper respiratory tract infection
Musculoskeletal and connective tissue disorders: back pain, arthralgia, pain in extremity, muscle spasms, musculoskeletal pain, joint swelling, neck pain, and myalgia
Nervous system disorders: hypoesthesia, pain, joint swelling, neck pain, and myalgia
Musculoskeletal and connective tissue disorders: back pain, arthralgia, pain in extremity, muscle spasms, musculoskeletal pain, joint swelling, neck pain, and myalgia
Nervous system disorders: hypoesthesia, pain, joint swelling, neck pain, and myalgia
Musculoskeletal and connective tissue disorders: back pain, arthralgia, pain in extremity, muscle spasms, musculoskeletal pain, joint swelling, neck pain, and myalgia
Nervous system disorders: hypoesthesia, pain, joint swelling, neck pain, and myalgia

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 dermatitis, asthma aggravated, bradycardia, chills, confusion state, contact dermatitis, coordination abnormal, dehydration, depersonalization, depressed level of consciousness, depressed mood, disorientation, disturbance in attention, diverticulitis, drug hypersensitivity, drug withdrawal syndrome, dry eye, dry skin, dysarthria, dysgeusia, dysphagia, euphoria mood, face edema, flatulence, flushing, gait disturbance, hallucination, hiccup, hot flush, hyperventilation, hypotension, hypoventilation, ileus, insomnia, libido decreased, loss of consciousness, malaise, memory impairment, mental impairment, mental status changes, miosis, muscle weakness, nervousness, nightmare, orthostatic hypotension, palpititations, psychotic disorder, respiration abnormal, respiratory depression, respiratory distress, respiratory failure, restlessness, rhinitis, sedation, sexual dysfunction, syncope, tachycardia, tinnitus, urinary hesitation, urinary incontinence, urinary retention, urticaria, vasodilation, 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)].

**7 DRUG INTERACTIONS**
Table 5 includes clinically significant drug interactions with BUTRANS.

### 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>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>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benzodiazepines and Other Central Nervous System (CNS) Depressants</th>
<th>Clinical Impact:</th>
<th>Intervention:</th>
</tr>
</thead>
<tbody>
<tr>
<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></td>
</tr>
</tbody>
</table>

| Examples: | Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol. |

<table>
<thead>
<tr>
<th>Inhibitors of CYP3A4</th>
<th>Clinical Impact:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<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>
<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>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples:</td>
<td>Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir)</td>
</tr>
</tbody>
</table>

**CYP3A4 Inducers**

**Clinical Impact:**

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.

**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

**Serotonergic Drugs**

**Clinical Impact:**

The concomitant use of opioidid with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

**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).

**Monoamine Oxidase Inhibitors (MAOIs)**

**Clinical Impact:**

MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see Warnings and Precautions (5.2)]

**Intervention:**

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

**Examples:**

- Phenelzine, tranylcypromine, linezolid

**Mixed Agonist/Antagonist Opioid Analgesics**

**Clinical Impact:**

May reduce the analgesic effect of BUTRANS and/or precipitate withdrawal symptoms.

**Intervention:**

Avoid concomitant use.

**Examples:**

- Butorphanol, nalbuphine, pentazocine

**Muscle Relaxants**

**Clinical Impact:**

Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

**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.

**Diuretics**

**Clinical Impact:**

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

**Intervention:**

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

**Anticholinergic Drugs**

**Clinical Impact:**

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.

**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 breastfeeding 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 in patients with severe hepatic impairment [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

BUTRANS contains buprenorphine, a Schedule III controlled substance.
9.2 Abuse
BUTRANS contains buprenorphine, a Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. BUTRANS can be abused and is subject to misuse, addiction and criminal diversion [see Warnings and Precautions (5.1)]. The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

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

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

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

“Drug-seeking” behavior is very common persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare providers(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

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

BUTRANS, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, is required 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, lacrimation, rhinorhea, 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. Dextromethorphan 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-((cyclopentylmethyl)-α-(1,1-dimethylhydroxyl) -4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-α-methyl-1, [5α, 7α, (S)]. The structural formula is:

The molecular weight of buprenorphine is 467.6; the empirical formula is C₃₉H₄₃NO₄. 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 6: BUTRANS Product Specifications

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<td>mcg/hour</td>
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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, 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 CLINICAL PHARMACOLOGY

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 (oxycodone 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 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).

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 reaplication 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 blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed. For this reason, instruct patients not to apply heating pads directly to the BUTRANS system during treatment [see Warnings and Precautions (5.14)].

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 mcg of buprenorphine were compared in 8 patients with mild impairment (Child-Pugh A), 4 patients with moderate impairment (Child-Pugh B) and 12 subjects with normal hepatic function. Buprenorphine and norbuprenorphine exposure did not increase in the mild and moderate hepatic impairment patients. BUTRANS has not been evaluated in patients with severe (Child-Pugh C) hepatic impairment. [see, 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 carcino- genic 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-naive 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-Naive 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 inadequate 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.

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](image)

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

During the double-blind period, patients were permitted to take ibuprofen (200 mg tablets) or acetaminophen (500 mg tablets) every 4 hours as needed for supplemental analgesia (up to 3200 mg of ibuprofen and 4 grams of acetaminophen daily). Sixty-seven percent of patients treated with BUTRANS 20 mcg/hour and 58% of patients treated with BUTRANS 5 mcg/hour completed the 12-week treatment. Of the 219 patients randomized to BUTRANS 20 mcg/hour, 11% discontinued due to lack of efficacy and 13% due to adverse events. Of the 221 patients randomized to BUTRANS 5 mcg/hour, 24% discontinued due to lack of efficacy and 6% due to adverse events.

Of the patients who were able to be randomized in the double-blind period, the mean pain (SE) NRS scores were 6.4 (0.08) and 6.5 (0.08) at screening and were 2.8 (0.08) and 2.9 (0.08) at pre-randomization (beginning of Double-Blind Period) for the BUTRANS 5 mcg/hour and BUTRANS 20 mcg/hour, respectively.

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

![Figure 4: Percent Reduction in Pain Intensity](image)

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 59011-751-04).

BUTRANS (buprenorphine) 15 mcg/hour Transdermal Systems are rectangular, 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 59011-758-04).

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 59011-752-04).

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

17 PATIENT COUNSELING INFORMATION

Advising 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)).

Interaction with 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 (see Drug Interactions (7)).

Serotonin Syndrome
Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications (see Drug Interactions 7).

MAO Interaction
Inform patients to avoid taking BUTRANS while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking BUTRANS (see Drug Interactions (7)).

Adrenal Insufficiency
Inform patients that opioids could cause 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
Inform 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 who may become pregnant of the potential for withdrawal symptoms in the neonate (see Warnings and Precautions (5.12)). Instruct patients of the need to use a contraceptive method during the use of BUTRANS (see Contraindications (4)).

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.

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Stamford, CT 06901-3431

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

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303385-0B BUP013
# Medication Guide

**BUTRANS® (BYOO-trans)**

(buprenorphine) transdermal system, CIII

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

**Important information about BUTRANS:**
- Get emergency help right away if you take too much BUTRANS (overdose). When you first start taking BUTRANS, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- 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
- heart rhythm problems (Long QT syndrome)
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

**Tell your healthcare provider if you:**
- have a fever
- are pregnant or planning to become pregnant. Prolonged use of BUTRANS during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- are breastfeeding. 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.
- are having or planning surgery.

**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](http://dailymed.nlm.nih.gov)

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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.

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

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

Figure M
3. Close the disposal unit by folding the sticky sides together (See Figure M).

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

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

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

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

Never put used BUTRANS patches in the trash without first sealing them in the Patch-Disposal Unit. This “Instructions for Use” has been approved by the U.S. Food and Drug Administration.

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