PRODUCT MONOGRAPH

^{N}BuTrans® 5
^{N}BuTrans® 10
^{N}BuTrans® 15
^{N}BuTrans® 20

Buprenorphine Transdermal System
5, 10, 15 and 20 mcg/h

Purdue Pharma Standard

Opioid Analgesic

Purdue Pharma
575 Granite Court
Pickering, Ontario
L1W 3W8

DATE OF REVISION:
August 5, 2016

Submission Control No: 194686

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[N]BuTrans®
Buprenorphine Transdermal System

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Transdermal	Patch Four strengths with 5, 10, 15 and 20 mg buprenorphine per patch, delivering 5, 10, 15 and 20 mcg/h buprenorphine respectively for 7 days	Aluminum acetylacetonate, levulinic acid, oleyl oleate, polyacrylate, polyethylene terephthalate, povidone

INDICATIONS AND CLINICAL USE

Adults

BuTrans® (buprenorphine transdermal patch) is indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and:

- that is opioid-responsive; and
- for which alternative options are inadequate.

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

Geriatrics (> 65 years of age)

In elderly patients, **BuTrans** may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance. Therefore, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy. Elderly patients should be initiated on the lowest available **BuTrans** strength (see **DOSAGE AND ADMINISTRATION**).

Pediatrics (< 18 years of age)

The safety and efficacy of **BuTrans** has not been studied in the pediatric population. Therefore, use of **BuTrans** is not indicated in patients under 18 years of age.

CONTRAINDICATIONS

BuTrans® (buprenorphine transdermal patch) is contraindicated in:

- Patients who are hypersensitive to this buprenorphine, other opioids, or to any ingredient in the formulation or component of the container. For a complete listing of excipients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph
- Patients who have ileus of any type
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis)
- Patients with mild, intermittent or short duration pain that can otherwise be managed
- The management of acute pain, including use in out-patient or day surgeries
- The management of peri-operative pain relief, or in other situations characterized by rapidly varying analgesic requirements (see **WARNINGS AND PRECAUTIONS**, **Perioperative Considerations**)
- Patients with acute asthma or other obstructive airway, and status asthmaticus
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale
- Patients with acute alcoholism or alcohol dependence, delirium tremens, and convulsive disorders
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy)
- Women during pregnancy, labour and delivery or breast-feeding
- Opioid dependent patients and for narcotic withdrawal treatment
- Patients suffering from myasthenia gravis
- Patients who have severe hepatic insufficiency

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with controlled release opioid formulations, BuTrans® (buprenorphine transdermal patch) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

BuTrans poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing BuTrans, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). BuTrans should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of BuTrans. Patients should be monitored for respiratory depression, especially during initiation of BuTrans or following a dose increase. Placing BuTrans patch in the mouth, chewing it, swallowing it or using it in any way other than indicated may cause choking or overdose that could result in death (see WARNINGS AND PRECAUTIONS).

Accidental Exposure

Serious medical consequences, including death, may occur if people, especially children, are accidentally exposed to BuTrans. Examples of accidental exposure include transfer of BuTrans while hugging, sharing a bed, or moving a patient (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of BuTrans during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

General

BuTrans should ONLY be prescribed to patients who require continuous opioids for pain management. Initiation doses higher than the 5 mg patch should not be used in opioid naïve

patients (see **DOSAGE AND ADMINISTRATION – Patients Not Already Taking Opioids [Opioid Naïve]**).

BuTrans should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain, and in the detection and management of respiratory depression including the use of opioid antagonists.

Since serum buprenorphine concentrations decline gradually after patch removal (approximately 50% in 12 hours [range 10-24 h]), patients who have experienced serious adverse events should be monitored for at least 24 hours after BuTrans removal or until the adverse reaction has subsided.

Due to the formation of a subcutaneous depot of buprenorphine, not only does continued exposure occur after patch removal but, in the case of removal prior to attainment of peak buprenorphine exposure, buprenorphine plasma levels may continue to increase after removal of BuTrans patches.

As with other CNS depressants, patients who have received BuTrans should be monitored especially for signs of respiratory depression until a stable maintenance dose is reached.

BuTrans patches are intended for transdermal use on intact skin only; use on compromised skin can lead to increased exposure to buprenorphine.

Patients should be cautioned not to consume alcohol while using **BuTrans** as it may increase the chance of experiencing dangerous side effects.

Risk of Unintentional Increase of Drug Exposure

Patients with Fever: A pharmacokinetic study showed no alteration of buprenorphine plasma concentrations in subjects with mild fever induced by endotoxin administration. However, because increased blood flow to the skin may enhance absorption, patients with severe febrile illness should be monitored for side effects and may require dose adjustment.

Application of External Heat: While wearing the **BuTrans** transdermal patch, patients should be advised to avoid exposing the **BuTrans** site to external heat sources, such as heating pads, electric blankets, heated water beds, heat or tanning lamps, hot water bottles, hot baths, saunas, hot whirlpool spa baths and sunbathing, as an increase in absorption of buprenorphine may occur and result in serious medical consequences.

Acute Abdominal Conditions

As with other μ-opioid receptor agonists, the administration of **BuTrans** may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Addiction, Abuse and Misuse

Like all opioids, **BuTrans** is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, **BuTrans** should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as **BuTrans**, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

BuTrans patches contain a large amount of a potent opioid, buprenorphine. The high buprenorphine content in **BuTrans** patches may be a target for abuse and diversion, with alternative routes of administration potentially resulting in overdose due to uncontrolled delivery of the opioid. This risk should be considered when prescribing or dispensing **BuTrans** in situations where the healthcare professional is concerned about increased risk of misuse, abuse or diversion.

Careful record keeping of prescribing information, including quantity, frequency, and renewal requests 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.

Carcinogenesis and Mutagenesis

See **TOXICOLOGY**.

Cardiovascular

Hypotensive Effects: BuTrans should be administered with caution to patients at risk for hypotension. Buprenorphine, like other opioids, may cause severe hypotension in patients with depleted blood volume or after agents acting on vasomotor tone such as phenothiazines or general anesthetics. Patients receiving **BuTrans** as their first around-the-clock opioid may be at increased risk of hypotension or orthostatic syncope, similar to that seen with other opioids.

Concomitant Use of CYP3A4 Inhibitors

The concomitant use of **BuTrans** with cytochrome P450 3A4 inhibitors such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, amiodarone, amprenavir, fosamprenavir, aprepitant, fluconazole, erythromycin and grapefruit juice may result in an increase in buprenorphine plasma concentrations, which could increase dose related toxicity, including potential fatal respiratory depression. In this situation, special patient care and observation is appropriate (see **DRUG INTERACTIONS**).

Concomitant Use of CYP3A4 Inducers

The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied. Co-administration of **BuTrans** and enzyme inducers (e.g., phenobarbital, carbamazepine, phenytoin, and rifampin) could lead to increased clearance which might result in reduced efficacy.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of **BuTrans** and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse. Buprenorphine is a partial μ-opioid agonist. Chronic use of buprenorphine can result in the development of a limited degree of physical dependence.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal (abstinence syndrome) may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. It is generally mild, begins after two days and may last up to two weeks. Reports of physical dependence and withdrawal syndrome with **BuTrans** treatment are uncommon.

BuTrans should not be prescribed to patients with known physical dependence on other opioids. Due to its antagonist component, **BuTrans** may not substitute for other opioids in such patients, as it may precipitate an abstinence syndrome depending on the level of physical dependence, and the timing and dose of buprenorphine. Caution should be exercised when prescribing **BuTrans** to patients known to have, or suspected of having, problems with other drug or alcohol abuse or serious mental illness.

All buprenorphine products have some potential for opioid abuse and dependence. However, reports of abuse with **BuTrans** in clinical trial and post marketing experience are uncommon.

Use in Drug Addiction

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

Hepatic/Biliary/Pancreatic

Because buprenorphine is extensively metabolized by the liver, the activity of **BuTrans** may be increased and/or extended in those individuals with impaired hepatic function or those receiving other agents known to decrease hepatic clearance. Patients with severe hepatic impairment may accumulate buprenorphine during **BuTrans** treatment. Consideration of alternate therapy should be given, and **BuTrans** should not be used in such patients (see **Special Populations**; **Hepatic Impairment**).

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and cause spasm of the Sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may also cause an increase in serum amylase concentration.

Immune

Allergic Reactions: Cases of acute and chronic hypersensitivity to buprenorphine have been reported in clinical trials in buprenorphine marketed products. The most common signs and symptoms include rashes, hives and pruritus.

Cases of bronchospasm, angioneurotic edema and anaphylactic shock have also been reported. A history of hypersensitivity to buprenorphine or any component of the formulation is a contraindication to **BuTrans** use.

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 to discontinue therapy.

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

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.

Use of **BuTrans** is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

In France, neonatal withdrawal has been reported in infants of women treated with sublingual buprenorphine for drug-addiction during pregnancy. Time to onset of withdrawal symptoms ranged from Day 1 to Day 8 of life with most occurring on Day 1 (69%). The most commonly-reported manifestations include abnormal crying, agitation, hypertonia, tremor and convulsions. Respiratory depression has occurred in neonates whose mothers had taken high doses, even for a short duration of time in the third trimester.

Neurologic

Interactions with Central Nervous System Depressants (including alcohol): BuTrans should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-

emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. Patients should be cautioned not to consume alcohol while using **BuTrans** as it may increase the chance of experiencing dangerous side effects (see **DRUG INTERACTIONS**).

Head Injury and Increased Intracranial Pressure: BuTrans should not be used in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, shock, or coma. Respiratory depression may be exacerbated in the presence of head injury, intracranial lesions (e.g., space occupying tumours) or increased intracranial pressure. Pupillary responses and effects on consciousness resulting from buprenorphine may mask neurologic signs of increasing intracranial pressure. Opioids may obscure the clinical course of patients with head injury.

Peri-operative Considerations

BuTrans is contraindicated for peri-operative pain relief, or in other situations characterized by rapidly varying analgesic requirements. In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with **BuTrans** for at least 48 hours before the operation and **BuTrans** should not be used in the immediate post-operative period. Thereafter if **BuTrans** is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated (see **Dependence/Tolerance**).

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist) (see **CONTRAINDICATIONS**).

Psychomotor Impairment

Opioid analgesics, including buprenorphine, can have a depressant effect on mental and/or physical responses. Caution must be exercised in activities requiring mental alertness such as driving a car or operating heavy machinery, especially when doses are being adjusted or when other CNS active drugs are being added to the treatment regimen. This impairment may be potentiated by concomitant depressant medications such as other opioids, phenothiazines, alcohol, sedatives, hypnotics, or other CNS depressants. Patients using **BuTrans** should not drive or operate dangerous machinery unless they are tolerant to the effects of the drug.

Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of **BuTrans**, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with **BuTrans** and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of **BuTrans** are essential (see **DOSAGE AND ADMINISTRATION**). Overestimating the **BuTrans** dose when converting patients from another opioid product can result in a fatal overdose with the first dose.

As with other potent opioids, clinically significant respiratory depression may occur in patients receiving buprenorphine. Some cases of death due to respiratory depression have been reported, particularly when addicts have intravenously abused buprenorphine, usually in combination with benzodiazepines, or with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Opioids, including buprenorphine, should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression), in the elderly and in debilitated patients. Particular caution is advised if **BuTrans** is to be administered to patients taking, or recently receiving, drugs with CNS/respiratory depressant effects.

IN THE CASE OF OVERDOSE, THE PRIMARY MANAGEMENT SHOULD BE THE REESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED. NALOXONE MAY NOT BE EFFECTIVE IN REVERSING ANY RESPIRATORY DEPRESSION PRODUCED BY BUPRENORPHINE (see OVERDOSAGE).

Although **BuTrans** is a partial opioid agonist, buprenorphine may cause hypoventilation at analgesic doses, especially in patients who have an underlying pulmonary condition or who receive usual doses of opioids or other CNS drugs associated with hypoventilation in addition to **BuTrans** (see **DRUG INTERACTIONS** regarding the use of concomitant CNS active drugs). Comparative effects of **BuTrans** have not been evaluated, but in clinical trials (up to doses of **BuTrans** 40 mcg/hr), respiratory failure was reported as a rare adverse event (i.e., <0.1%, but at least in more than 1 patient [see **ADVERSE REACTIONS]**).

If respiratory depression from **BuTrans** occurs, it may persist beyond the removal of the patch. Patients with hypoventilation should be observed for at least several hours and until their respiratory rate has recovered.

In patients with respiratory depression, symptomatic treatment following standard intensive care measures should be instituted (see **OVERDOSAGE**).

Use in Patients with Chronic Pulmonary Disease: Buprenorphine should be used with caution in patients with chronic pulmonary disease, patients with decreased respiratory reserve and others with potentially compromised respiration. Normal analgesic doses of opioids may further decrease respiratory drive in these patients to the point of respiratory failure.

Patient Counselling Information

A patient information sheet is included in the package of **BuTrans** patches dispensed to the patient.

Patients receiving **BuTrans** patches should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.
2. Patients should be advised that **BuTrans** patches contain buprenorphine, an opioid pain medicine.
3. Patients should be advised that each **BuTrans** patch should be worn continuously for 7 days. After 7 days, the old patch should be removed prior to applying a new patch.
4. Patients are advised not to apply more than one patch at the same time unless prescribed by your doctor. If two patches are prescribed, the patches should be applied at the same time and at the same site right next to each other. Always apply and remove the two patches together at the same time. The maximum total dose cannot exceed 20 mcg/h.
5. Patients should be advised that the application area should be rotated whenever a patch is replaced. A 3-week interval is required before the same area can be re-used as a strategy to prevent skin irritation and/or reduce the potential for increased drug absorption. After 3 weeks, when returning to a previously used area, patients should vary the skin site used within the area if possible.
6. Patients should be advised that **BuTrans** patches should be applied to intact, non-irritated and non-irradiated skin on a flat surface such as the upper chest, upper back, side of chest, or upper outer arm. Additionally, patients should be advised of the following:
   - If **BuTrans** is part of an overall strategy to suitably manage pain in patients with cognitive impairment, the potential of each patient to remove the patch(es) and place them in the mouth or on others should be considered when recommending rotation sites;
   - Hair at the application site should be clipped (not shaved) prior to patch application;
   - If the site of **BuTrans** application must be cleansed prior to application of the patch, do so with clear water;
   - Allow the skin to dry completely prior to patch application;
   - Do not use soaps, oils, lotions, alcohol, or any other agents that may irritate the skin or alter its characteristics.
7. Patients should be advised that **BuTrans** should be applied immediately upon removal from the sealed package and after removal of the protective liner. Additionally, patients should be advised of the following:
   - The **BuTrans** patch should not be used if the seal is broken, or if it is altered, cut, or damaged in any way prior to application. The transdermal patch should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges;

- The patch should **not** be folded.

8. Patients should be advised that while wearing the patch, they should avoid exposing the **BuTrans** application site to direct external heat sources, such as:

   - heating pads;
   - electric blankets;
   - heat lamps;
   - saunas;
   - hot tubs;
   - heated water beds.

9. Patients should be advised that there is a potential for temperature-dependent increase in buprenorphine release from the patch that could result in an overdose of buprenorphine. If patients develop a high fever while wearing the patch they should contact their physician.

10. Patients should be advised that if they experience problems with adhesion of the **BuTrans** patch, they may tape the edges of the patch with first aid tape.

11. Patients should be advised that if the patch falls off before 7 days a new patch may be applied to a different skin site. If two patches were applied and one falls off, remove the second patch on the body, discard both and apply two new patches next to each other on a different skin site.

12. When **BuTrans** is no longer needed (used or unused), patients should be advised to fold the patch (so that the adhesive side adheres to itself) and discard it (consult with a pharmacist about disposal options).

13. Patients should be instructed that, if the drug adhesive layer accidentally contacts the skin other than the intended application site, the area should be washed clean with clear water and not soap, alcohol, or other chemicals, because these products may increase the ability of buprenorphine to go through the skin.

14. Patients should be advised that the dose of **BuTrans** should NEVER be adjusted without the prescribing health care professional's instruction.

15. Patients should be advised that **BuTrans** may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).

16. Patients should be advised to refrain from any potentially dangerous activity when initially starting on **BuTrans** or when their dose is being adjusted, until it is established that they have not been adversely affected.

17. Patients should be advised that **BuTrans** should not be combined with alcohol or other centrally acting agents, such as: sleep medications, tranquilizers, sedatives and hypnotics because dangerous additive effects may occur, resulting in serious injury or death.

18. Patients should be advised to consult their physician or pharmacist if other medications are being, or will be, used with **BuTrans**.

19. Patients should be advised of the potential for severe constipation.

20. Patients should be advised that if they have been receiving treatment with **BuTrans** and cessation of therapy is indicated, it may be appropriate to taper the **BuTrans** dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Withdrawal symptoms are generally milder than seen with full agonists, and begin after two days and may last up to two weeks.
21. Patients should be advised that **BuTrans** contains buprenorphine, a drug with a potential for abuse.
22. Patients, family members and caregivers should be advised to protect **BuTrans** from theft or misuse in the work or home environment.
23. Patients should be advised that **BuTrans** should never be given to anyone other than the individual for whom it was prescribed because of the risk of death or other serious medical problems to that person, for whom it was not intended.
24. Patients should be instructed to keep **BuTrans** in a secure place out of sight and reach of children due to the risk of fatal respiratory depression.
25. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with **BuTrans**.
26. Patients should be informed that, if the patch dislodges and accidentally sticks to the skin of another person, they should immediately take the patch off, wash the exposed area with water (and not soap, alcohol, or other chemicals, because these products may increase the ability of buprenorphine to go through the skin) and seek immediate medical attention for the accidentally exposed individual.

Special Populations

Special Risk Groups: Use of **BuTrans**, like all opioid analgesics, is associated with increased potential risks and should be used only with caution in the following conditions: adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; high-risk debilitated patients; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture, and toxic psychosis.

The administration of buprenorphine, like other opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Buprenorphine may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings.

Pregnant Women: Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS**, **Neonatal Opioid Withdrawal Syndrome**). Buprenorphine crosses the placental barrier and has been detected in newborn blood, urine and meconium. Use of **BuTrans** is contraindicated in pregnant women (**see CONTRAINDICATIONS**). **BuTrans** should not be used in women of childbearing potential who are not using effective contraception unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Labour and Delivery: **BuTrans** is contraindicated during labour and delivery (see **CONTRAINDICATIONS**).

Nursing Women: Buprenorphine has been detected in low concentrations in human milk. **BuTrans** is contraindicated in breast-feeding women (see **CONTRAINDICATIONS**).

Gender: No differences in plasma buprenorphine concentrations were detected between males and females treated with **BuTrans**.

Geriatrics (> 65 years of age): The pharmacokinetic profile of **BuTrans** is similar in healthy elderly and younger adult subjects. Elderly subjects trended toward higher plasma concentrations of buprenorphine immediately after removal of **BuTrans**. In a pharmacokinetic study in healthy volunteers, mean plasma concentrations changed from 88.11 pg/mL at the time of patch removal at steady state to a peak of 90.77 pg/mL one hour after patch removal in younger adults (n=12). By three hours after patch removal, mean plasma levels had declined to less than 88.11 pg/mL (i.e., 73.76 pg/mL).

Mean plasma concentrations in healthy elderly adults (n=12) changed from 90.68 pg/mL at patch removal to a peak of 99.56 pg/mL 12 hours after patch removal. By 18 hours after patch removal, mean plasma concentrations had declined to less than 90.68 pg/mL (i.e., 84.18 pg/mL) in healthy elderly adults. Both groups subsequently eliminated buprenorphine at similar rates.

In a safety study evaluating the recommended dose-escalation schedule, the pharmacokinetics in healthy elderly were similar to healthy younger adults.

Pediatrics (< 18 years of age): **BuTrans** has not been studied in children and is not indicated for patients less than 18 years of age. The safety and efficacy of **BuTrans** in children have not been studied.

Renal Impairment: A pharmacokinetic study showed that pharmacokinetic parameters for buprenorphine were similar in patients with severe renal impairment compared with normal adults. This study confirmed with multiple-dose use, that the accumulation of buprenorphine metabolites did not decrease the clearance of the parent molecule in chronic use. Therefore, no special dose adjustment of buprenorphine is necessary in patients with renal impairment.

Hepatic Impairment: In a pharmacokinetic study utilizing intravenous buprenorphine, there were no differences in clearance of buprenorphine between mild to moderate hepatically impaired subjects relative to healthy adult subjects. These data show no need for dosage adjustment when using **BuTrans** in patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment may accumulate buprenorphine during **BuTrans** treatment. Consideration of alternate therapy should be given, and **BuTrans** should not be used in such patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Serious adverse drug reactions which may be associated with **BuTrans®** (buprenorphine transdermal patch) therapy in clinical use are those observed with other opioid analgesics, including respiratory depression (especially when used with other CNS depressants) and hypotension. Care must be exercised when using **BuTrans** in patients who are using benzodiazepines or other agents with CNS activity.

The adverse drug reactions seen on initiation of therapy with **BuTrans** in clinical studies are those often observed with other opioid analgesics (nausea, vomiting, dizziness, somnolence, constipation, pruritus and dry mouth). The frequency of these events depends on the dose, the clinical setting, the patient's level of opioid tolerance, and factors specific to the individual. They should be expected and managed as part of opioid analgesic therapy.

The most common adverse effects in six randomized titration-to-effect placebo-controlled clinical trials with **BuTrans** were anorexia, application site erythema, application site reactions, asthenia, constipation, dizziness, dry mouth, headache, hyperhidrosis, insomnia, nausea, somnolence and vomiting. Opioid-agonist related adverse events tend to reduce over time, except for constipation.

A summary of adverse events for the randomized parallel-design titration-to-effect placebo controlled clinical trials occurring at an incidence of ≥1% is provided in Table 1. A summary of adverse events for the randomized crossover-design titration-to-effect placebo controlled clinical trials occurring at an incidence of ≥1% is provided in Table 2. A summary of adverse events, occurring at an incidence of ≥1% in a clinical trial in patients shown to be tolerant and responsive to a **BuTrans (**5 - 20 mcg/h) patch during a run-in period of 3 weeks maximum, prior to randomization is provided in Table 3**.** The Tables include all events which occurred more frequently with active treatment than with placebo, whether considered by the clinical investigator to be related to the study drug or not. A summary of the less common clinical trial adverse events follows these Tables.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event regardless of causality. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Table 1: Adverse Events ≥ 1% for Parallel-Design Titration-to-Effect Clinical Trials (BP96-0604, BP99-0203, BP98-1201, BUP3002)

SOC MedDRA Preferred Term	BuTrans (N = 392)	Placebo (N = 261)
Ear and Labyrinth Disorders		
Tinnitus	1.3	0.4
Eye Disorders		
Vision blurred	1.5	0.4
Gastrointestinal Disorders		
Constipation	13.5	5.4
Diarrhea	3.1	1.9
Dry mouth	7.1	1.5
Nausea	22.7	7.7
Stomach discomfort	2.0	1.1
Vomiting	11.2	1.5
General Disorders and Administration Site Conditions		
Application site erythema	7.1	1.5
Application site pain	1.5	0.8
Application site pruritus	15.1	11.9
Application site vesicles	1.0	0.0
Asthenia	1.3	1.1
Fatigue	5.1	1.1
Pain	1.5	1.5
Peripheral edema	7.4	3.4
Pyrexia	1.5	0.4
Infections and Infestations		
Influenza	1.3	0.4
Sinusitis	1.0	0.4
Urinary tract infection	2.6	2.3
Injury, Poisoning and Procedural Complications		
Fall	3.8	1.5
Skin Laceration	1.3	1.1
Investigations		
Blood pressure increased	1.0	0.4
Metabolism and Nutrition Disorders		
Anorexia	2.0	0.8
Musculoskeletal and		

Table 1: Adverse Events ≥ 1% for Parallel-Design Titration-to-Effect Clinical Trials (BP96-0604, BP99-0203, BP98-1201, BUP3002)

SOC MedDRA Preferred Term	BuTrans (N = 392)	Placebo (N = 261)
Connective Tissue Disorders		
Arthralgia	2.0	1.9
Back pain	2.6	1.5
Joint swelling	2.6	0.8
Muscle spasms	1.3	0.8
Muscular weakness	1.0	0.4
Pain in extremity	2.8	2.3
Nervous System Disorders		
Dizziness	16.3	7.7
Headache	16.1	11.5
Hypoesthesia	2.3	0.8
Migraine	1.0	0.8
Paraesthesia	2.0	0.8
Tremor	2.0	0.4
Somnolence	13.5	4.6
Psychiatric Disorders		
Agitation	1.0	0.0
Anxiety	1.8	0.8
Depression	1.3	0.8
Disorientation	1.0	0.4
Insomnia	2.8	1.9
Nervousness	1.0	0.4
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.3	0.4
Dyspnea	2.8	1.1
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	4.3	1.1
Pruritus	4.1	0.8
Pruritus generalized	1.5	0.8
Rash	2.0	1.1

Table 2: Adverse Events ≥1% for Crossover-Design Titration-to-Effect Clinical Trials (020-006 and 020-007)

SOC MedDRA Preferred Term	BuTrans (N = 146)	Placebo (N = 133)
Cardiac Disorders		
Palpitations	3.4	0.8
Ear and Labyrinth Disorders		
Tinnitus	1.4	0.0
Vertigo	1.4	0.0
Gastrointestinal Disorders		
Abdominal pain upper	3.4	2.3
Constipation	21.9	13.5
Dry mouth	10.3	1.5
Gastroesophageal reflux disease	1.4	0.0
Nausea	45.9	18.0
Vomiting	18.5	4.5
General Disorders and Administration Site Conditions		
Application site bruising	1.4	0.0
Application site pain	2.1	1.5
Application site pruritus	25.3	24.8
Application site rash	3.4	3.0
Asthenia	12.3	8.3
Fatigue	9.6	3.0
Influenza-like illness	2.1	0.0
Peripheral edema	8.9	0.8
Immune System Disorders		
Urticaria	1.4	0.0
Infections and Infestations		
Influenza	2.1	1.5
Urinary tract infection	2.1	0.8
Metabolism and Nutrition Disorders		
Anorexia	13.0	11.3
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal stiffness	1.4	0.8
Myalgia	2.1	0.0
Nervous System Disorders		
Dizziness	27.4	6.0
Headache	11.6	6.0
Migraine	2.7	1.5
Paraesthesia	1.4	0.8

Table 2: Adverse Events ≥1% for Crossover-Design Titration-to-Effect Clinical Trials (020-006 and 020-007)

SOC MedDRA Preferred Term	BuTrans (N = 146)	Placebo (N = 133)
Somnolence	24.0	6.0
Tremor	4.1	2.3
Psychiatric Disorders		
Agitation	2.7	1.5
Anxiety	2.1	0.8
Nightmare	1.4	0.8
Skin and Subcutaneous Tissue Disorders		
Erythema	1.4	0.0
Hyperhidrosis	16.4	9.0
Pruritus	1.4	0.8
Surgical and Medical Procedures		
Endodontic procedure	1.4	0.0
Vascular Disorders		
Hot flush	4.1	1.5

Table 3: Adverse Events ≥ 1% for Patients shown to be Tolerant and Responsive to a BuTrans (5 - 20 mcg/h) Patch during a Run-in Period of 3 Weeks Maximum, Prior to Randomization (Study BUP3012)

SOC MedDRA Preferred Term	BuTrans (N = 164)	Placebo (N = 162)
Gastrointestinal Disorders		
Abdominal pain	1.2	0.0
Constipation	7.1	5.2
Diarrhea	1.5	1.5
Dry mouth	2.8	2.1
Nausea	8.9	8.9
Vomiting	2.1	0.9
General Disorders and Administration Site Conditions		
Application site erythema	3.1	1.5
Application site pruritus	4.6	3.4
Application site rash	2.1	0.6
Fatigue	2.5	1.5
Peripheral edema	3.4	0.6

Table 3: Adverse Events ≥ 1% for Patients shown to be Tolerant and Responsive to a BuTrans (5 - 20 mcg/h) Patch during a Run-in Period of 3 Weeks Maximum, Prior to Randomization (Study BUP3012)

SOC MedDRA Preferred Term	BuTrans (N = 164)	Placebo (N = 162)
Infections and Infestations		
Urinary tract infection	1.2	0.3
Musculoskeletal and Connective Tissue Disorders		
Back pain	2.5	2.1
Pain in extremity	1.2	1.2
Nervous System Disorders		
Dizziness	6.1	3.7
Psychiatric Disorders		
Anxiety	1.2	0.3

In clinical trials in which **BuTrans** was compared to active controls, expected opioid effects (nausea, vomiting, dry mouth, pruritus, dizziness, somnolence), on initiation of therapy in non-tolerant individuals, reached their maximum 1 - 2 days after **BuTrans** application and usually decreased with continued use.

Less Common Clinical Trial Adverse Drug Reactions

Untoward events associated with the exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

Reported adverse events were classified using the Medical Dictionary for Regulatory Activities, version 10.0.

The events listed below present treatment emergent adverse events reported during the clinical development program of buprenorphine in a total of 5,561 patients in the Phase 3 controlled and open-label clinical trials. Excluded from this list are those events already listed in Table 1 – Table 3.

It is important to emphasize that, although the events reported occurred during treatment with buprenorphine, they were not necessarily caused by it. The events are categorized by body system and listed according to the following criteria: frequent: adverse events that occurred on one or more occasions in at least 1/100 patients; infrequent: adverse events that occurred in less than 1/100 patients but at least in 1/1000 patients; and rare: adverse events that occurred in less than 1/1000, but in at least more than 1 patient.

Blood and Lymphatic System Disorders:

Infrequent: Anemia, lymphadenopathy.

Rare: Leukocytosis.

Cardiac Disorders:

Infrequent: Angina pectoris, atrial fibrillation, bradycardia, cardiac failure congestive, myocardial infarction, tachycardia.

Rare: Acute coronary syndrome, acute myocardial infarction, angina unstable, arrhythmia, atrioventricular block first degree, bundle branch block left, cardiac flutter, cardiomegaly, coronary artery disease, extrasystoles, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles.

Ear and Labyrinth Disorders:

Infrequent: Cerumen impaction, ear pain.

Rare: Ear discomfort, ear haemorrhage, inner ear disorder, middle ear effusion, otorrhoea, tympanic membrane hyperaemia.

Endocrine Disorders:

Rare: Hyperthyroidism, hypothyroidism.

Eye Disorders:

Infrequent: Cataract, conjunctivitis, dry eye, eye pruritus, eye swelling, vision blurred.

Rare: Asthenopia, blepharospasm, conjunctival haemorrhage, diplopia, eye disorder, eye irritation, eye pain, eyelid irritation, lacrimation increased, lenticular opacities, miosis, myopia, ocular hyperaemia, photopsia, visual acuity reduced, visual disturbance.

Gastrointestinal Disorders:

Frequent: Dyspepsia.

Infrequent: Abdominal discomfort, abdominal distension, abdominal pain lower, colonic polyp, dental caries, dysphagia, flatulence, food poisoning, gastric ulcer, gastritis, haemorrhoids, lip swelling, oral pain, rectal haemorrhage, toothache.

Rare: Abdominal haematoma, abdominal hernia, abdominal mass, abdominal tenderness, colitis, Crohn's disease, diverticulum, eructation, faeces discoloured, faeces hard, frequent bowel movements, gastrointestinal haemorrhage, gastrointestinal pain, gingival pain, haematochezia, haemorrhoidal haemorrhage, hiatus hernia, hypoaesthesia oral, ileus, inguinal hernia, intestinal obstruction, irritable bowel syndrome, mouth ulceration, oesophageal spasm, oral discomfort, oral mucosal blistering, pancreatitis, paraesthesia oral, peptic ulcer, retching, stomatitis, swollen tongue, tooth disorder, umbilical hernia.

General Disorders and Administration Site Conditions:

Frequent: Application site irritation, chest pain.

Infrequent: Application site dermatitis, application site discharge, application site discolouration, application site dryness, application site excoriation, application site exfoliation,

application site inflammation, application site oedema, application site papules, application site paraesthesia, application site reaction, application site scab, application site swelling, chest discomfort, chills, drug withdrawal syndrome, energy increased, feeling abnormal, feeling hot, feeling jittery, gait disturbance, irritability, malaise, oedema, thirst.

Rare: Application site anaesthesia, application site bleeding, application site hypersensitivity, application site induration, application site odour, application site perspiration, application site urticaria, application site warmth, axillary pain, cyst, discomfort, face oedema, facial pain, feeling cold, feeling hot and cold, feeling of relaxation, generalised oedema, hernia, hunger, inadequate analgesia, inflammation, inflammatory pain, local swelling, lower extremity mass, pitting oedema, pre-existing condition improved, sensation of pressure, sluggishness, swelling, temperature intolerance, therapeutic response unexpected.

Hepatobiliary Disorders:

Rare: Biliary colic, cholecystitis, cholecystitis acute, cholelithiasis, gallbladder disorder.

Immune System Disorders:

Infrequent: Allergic reaction (including oropharyngeal swelling and swollen tongue), hypersensitivity, seasonal allergy.

Rare: Drug hypersensitivity.

Infections and Infestations:

Frequent: Bronchitis, nasopharyngitis, upper respiratory tract infection.

Infrequent: Application site pustules, cellulitis, cystitis, diverticulitis, ear infection, eye infection, folliculitis, fungal infection, gastroenteritis, gastroenteritis viral, herpes zoster, kidney infection, laryngitis, localised infection, lower respiratory tract infection, oral herpes, otitis media, pharyngitis, pharyngitis streptococcal, pneumonia, tooth abscess, tooth infection, viral infection.

Rare: Abscess, application site cellulitis, application site infection, body tinea, fungal skin infection, furuncle, gingival infection, Helicobacter infection, Herpes simplex, infected sebaceous cyst, labyrinthitis, lobar pneumonia, mastoiditis, onychomycosis, oral candidiasis, oral fungal infection, osteomyelitis, otitis externa, respiratory tract infection, rhinitis, sepsis, skin candida, Staphylococcal infection, tinea pedis, tonsillitis, vaginal candidiasis, vaginal infection, viral upper respiratory tract infection, vulvovaginal mycotic infection, vulvovaginitis, wound infection.

Injury, Poisoning and Procedural Complications:

Infrequent: Arthropod bite, back injury, contusion, excoriation, foot fracture, injury, joint dislocation, joint injury, joint sprain, limb injury, muscle strain, procedural pain, road traffic accident, thermal burn.

Rare: Accident, animal bite, arthropod sting, bite, concussion, corneal abrasion, epicondylitis, eye injury, facial bones fracture, foreign body in eye, hand fracture, head injury, hip fracture, laceration, ligament rupture, lower limb fracture, medical device site reaction, meniscus lesion,

mouth injury, neck injury, rib fracture, scratch, skeletal injury, sunburn, tooth fracture, upper limb fracture, whiplash injury, wrist fracture.

Investigations:

Infrequent: Alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, blood glucose increased, blood potassium decreased, blood potassium increased, blood sodium decreased, blood triglycerides increased, blood urea increased, blood uric acid increased, blood urine present, body temperature increased, cardiac murmur, glucose urine present, haematocrit decreased, haemoglobin decreased, heart rate increased, liver function test abnormal, weight decreased, weight increased, white blood cell count increased.

Rare: Blood alkaline phosphatase increased, blood bilirubin increased, blood chloride decreased, blood cholesterol increased, blood glucose decreased, blood lactate dehydrogenase increased, blood pressure decreased, blood pressure diastolic increased, blood stimulating hormone, body temperature fluctuation, breath sounds abnormal, carbon dioxide decreased, electrocardiogram QT corrected interval, electrocardiogram T wave abnormal, eosinophil count decreased, gamma-glutamyltransferase increased, gastric pH decreased, haemoglobin increased, heart rate irregular, Helicobacter pylori identification, hepatic enzyme increased, lymphocyte count increased, neutrophil count decreased, platelet count decreased, platelet count increased, prostate examination abnormal, protein urine present, red blood cell count decreased, respiratory rate decreased, urine analysis, abnormal, urine ketone body present, urine output decreased, white blood cells urine positive.

Metabolism and Nutrition Disorders:

Infrequent: Decreased appetite, dehydration, diabetes mellitus, fluid retention, gout, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hypokalaemia.

Rare: Diabetes mellitus inadequate control, diabetes mellitus non insulin-dependent, electrolyte imbalance, hyperkalaemia, hyperphagia, hypertriglyceridaemia, hyperuricaemia, hypoglycaemia, hyponatraemia, hypovolaemia, increased appetite, lactose intolerance, malnutrition.

Musculoskeletal and Connective Tissue Disorders:
Frequent: Musculoskeletal pain, neck pain.

Infrequent: Arthritis, bone pain, bursitis, costochondritis, exostosis, flank pain, groin pain, intervertebral disc protrusion, joint crepitation, joint range of motion decreased, joint stiffness, muscle twitching, musculoskeletal chest pain, osteoarthritis, pain in jaw, rotator cuff syndrome, tendonitis.

Rare: Arthropathy, bunion, coccydynia, fibromyalgia, joint effusion, lumbar spinal stenosis, muscle tightness, musculoskeletal discomfort, musculoskeletal disorder, osteoporosis, periarthritis, plantar fasciitis, rheumatoid arthritis, sensation of heaviness, synovial cyst, trigger finger.

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps):

Rare: Basal cell carcinoma, benign breast neoplasm, lipoma seborrheic keratosis, skin cancer.

Nervous System Disorders:

Infrequent: Amnesia, balance disorder, burning sensation, carpal tunnel syndrome, coordination abnormal, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment, mental impairment, neuropathy peripheral, sciatica, sedation, sinus headache, syncope, tension headache, transient ischaemic attack.

Rare: Ageusia, carotid artery stenosis, cerebrovascular accident, convulsion, depressed level of consciousness, dizziness postural, facial palsy, formication, hyperaesthesia, hypersomnia hyporeflexia nerve compression, neuralgia, neuropathy, poor quality sleep, presyncope, restless legs syndrome, subarachnoid haemorrhage.

Psychiatric Disorders:

Infrequent: Abnormal dreams, confusional state, depersonalisation, depressed mood, euphoric mood, hallucination, libido decreased, mood swings, panic attack.

Rare: Affect lability, anorgasmia, anxiety disorder, crying, delirium, initial insomnia, listless, loss of libido, major depression, mood altered, nicotine dependence, paranoia, psychotic disorder, restlessness, sleep disorder, stress, tension, thinking abnormal, tic.

Renal and Urinary Disorders:

Infrequent: Dysuria, haematuria, micturition urgency, nephrolithiasis, pollakiuria, urinary hesitation, urinary retention.

Rare: Acute prerenal failure, bladder spasm, chromaturia, incontinence, micturition frequency decreased, nocturia, polyuria, proteinuria, renal cyst, renal failure, renal failure acute, renal pain, urinary incontinence.

Reproductive System and Breast Disorders:

Infrequent: Breast mass, dysmenorrhoea, erectile dysfunction.

Rare: Benign prostatic hyperplasia, breast discharge, breast pain, breast tenderness, ejaculation delayed, ejaculation disorder, ejaculation failure, genital rash, menstruation irregular, metrorrhagia, pelvic pain, priapism, prostatic disorder, prostatitis, sexual dysfunction, vaginal discharge, vaginal haemorrhage.

Respiratory, Thoracic and Mediastinal Disorders:

Frequent: Pharyngolaryngeal pain.

Infrequent: Asthma, chronic obstructive pulmonary disease, epistaxis, hiccups, hyperventilation, hypoxia, nasal congestion, respiratory disorder, respiratory tract congestion, rhinitis allergic, rhinorrhea, sinus congestion, sneezing, upper respiratory tract congestion, wheezing, yawning.

Rare: Allergic sinusitis, bronchospasm, dry throat, dysphonia, dyspnoea exertional, emphysema, nasal discomfort, nasal dryness, paranasal sinus hypersecretion, pharyngeal erythema, pleural effusion, postnasal drip, productive cough, pulmonary embolism, pulmonary hypertension, pulmonary oedema, rales, respiratory failure, rhonchi, sinus disorder, throat irritation, throat tightness.

Skin and Subcutaneous Tissue Disorders:

Infrequent: Acne, alopecia, blister, cold sweat, dermatitis, dermatitis allergic, dermatitis contact, dry skin, eczema, night sweats, psoriasis, rash erythematous, rash generalised, rash papular, rash pruritic, skin irritation, skin lesion, swelling face.

Rare: Angioedema, decubitus ulcer, dermal cyst, ecchymosis, heat rash, hyperkeratosis, hypoaesthesia facial, ingrowing nail, petechiae, piloerection, rash macular, skin burning sensation, skin discolouration, skin exfoliation, skin ulcer.

Very rare: Pustules, vesicles.

Social Circumstances:

Infrequent: Drug abuser.

Rare: Menopause.

Surgical and Medical Procedures:

Rare: Knee arthroplasty, tooth extraction, tooth repair.

Vascular Disorders:

Frequent: Hypertension, vasodilatation.

Infrequent: Flushing, haematoma, hypotension.

Rare: Aortic aneurysm, deep vein thrombosis, hypertensive crisis, orthostatic hypotension, pallor, varicose vein.

Post-Market Adverse Drug Reactions

In addition to adverse events reported from clinical trials, the following events have been identified during post-market use of **BuTrans**. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency.

General Disorders and Administration Site Conditions:
Drug withdrawal syndrome neonatal

Immune System Disorders:
Anaphylactic responses

Psychiatric Disorders:
Aggression

DRUG INTERACTIONS

Overview

Additive Effects of Other CNS Depressants: BuTrans® (buprenorphine transdermal patch) should be dosed with caution in patients who are currently taking other CNS depressants or other drugs that may cause respiratory depression, hypotension, profound sedation, or may potentially result in coma. Such agents include antihistamines, antipsychotics, anxiolytics, barbiturates, benzodiazepines, centrally acting anti-emetics, clonidine and related substances, general anaesthetics, neuroleptics, other opioid derivatives (analgesic and antitussive), phenothiazines and sedatives or hypnotics. When such combined therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients carefully monitored (see **WARNINGS AND PRECAUTIONS, Neurologic – Interaction with Other Central Nervous System Depressants**). Patients should also be warned that these combinations increase central nervous system depression and can make driving vehicles and operating machinery hazardous (see **WARNINGS AND PRECAUTIONS, Psychomotor Impairment**).
Patients should be cautioned not to consume alcohol while using **BuTrans** as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

CYP 3A4 Inhibitors: Buprenorphine is primarily metabolized by glucuronidation and to a lesser extent (about 30%) by CYP3A4. Concomitant treatment with CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, amiodarone, amprenavir, fosamprenavir, aprepitant, fluconazole, erythromycin and grapefruit juice) may lead to elevated plasma concentrations with an increase in dose related toxicity of buprenorphine including potentially fatal respiratory depression (see **WARNINGS AND PRECAUTIONS, Concomitant Use of CYP3A4 Inhibitors**). The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied. Co-administration of **BuTrans** and enzyme inducers (e.g., phenobarbital, carbamazepine, phenytoin, and rifampin) could lead to increased clearance which might result in reduced efficacy.

MAO Inhibitors: MAO inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. Buprenorphine is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS**).

Warfarin: The potential may exist for INR elevation in patients who are concomitantly taking warfarin.

Anesthetics: Reductions in hepatic blood flow induced by some general anesthetics (e.g., halothane) and other drugs may result in a decreased rate of hepatic elimination of buprenorphine.

Flunitrazepam: Deaths have been reported in the addict population when buprenorphine was co-administered with flunitrazepam. This adverse drug interaction cannot be explained by a pharmacokinetic drug-drug interaction. Caution must be exercised with the combined use of

buprenorphine and flunitrazepam and a dosage reduction in one or both drugs should be considered.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS**, **General**).

DOSAGE AND ADMINISTRATION

BuTrans® (buprenorphine transdermal patch) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated, or would be otherwise inadequate to provide appropriate management of pain.

Placing **BuTrans** patch in the mouth, chewing it, swallowing it or using it in any ways other than indicated may cause choking or overdose that could result in death (see **WARNINGS AND PRECAUTIONS**).

BuTrans should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain, and in the detection and management of respiratory depression including the use of opioid antagonists.

Recommended Dose and Dosage Adjustment

BuTrans is intended to be used for the continual release of buprenorphine transdermally over a 7-day period per patch. **BuTrans** can be used in either opioid naïve patients or patients previously treated with PRN (as needed) analgesics when the analgesic requirement has progressed to a need for continuous opioid analgesia.

BuTrans doses must be individualized based upon the status of each patient and should be assessed at regular intervals after application. Proper optimization of doses scaled to the relief of the individual's pain should aim at the regular administration of the lowest dose of **BuTrans** which provides pain relief with acceptable side effects. The dosage of the drug must be individualized according to the response and tolerance of the patient. An important factor to be considered in determining the appropriate dose is the extent of pre-existing opioid tolerance (see **Conversion from Opioid or Fixed-Ratio Opioid/Non-Opioid Combination Drugs**). Initiation on the lowest available strength of **BuTrans** with appropriate dose titration is suggested for the elderly and other groups discussed in **WARNINGS AND PRECAUTIONS**.

The patch should be worn for 7 days continuously before changing to a new patch at the same dose. A new skin area should be selected when changing to a new patch. After the patch is removed, a 3-week interval is required before the same area can be re-used. When returning to a previously used area, after at least 3 weeks, a different skin site should be used if possible. (See **PATIENT MEDICATION INFORMATION – How to Use BuTrans**).

BuTrans should not be used in individuals less than 40 kg in weight. **BuTrans** may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance.

Opioid analgesics may be only partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with these types of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

BuTrans has potential for abuse and diversion (see **WARNINGS AND PRECAUTIONS**).

Initial BuTrans Dose Selection

BuTrans is designed to allow for once weekly dosing, i.e., dosing every 7 days. Treatment with **BuTrans** should generally be initiated at the lowest available dose (**BuTrans 5**).

Patients Not Already Taking Opioids (Opioid-Naïve)

In situations when it is clinically indicated to initiate opioid therapy with a maintenance (around-the-clock) opioid in an opioid naïve patient, clinical trials have shown that such patients may successfully initiate opioid therapy with **BuTrans**. **The lowest dose available (BuTrans 5) should always be used as the initial dose and titrated as required. If the patient requires rescue medication, see Management of Patients Requiring Rescue Medication section**.

Conversion from Opioid or Fixed-Ratio Opioid/Non-Opioid Combination Drugs

BuTrans has been studied as an alternative opioid analgesic in patients taking up to 80 mg of oral morphine-equivalents a day. Such patients should be started on **BuTrans 5** or **BuTrans 10** and be provided with adequate rescue medication and titrated as required (see **Management of Patients Requiring Rescue Medication**).

Patch Application

BuTrans should be applied to non-irritated, intact skin of the upper outer arm, upper chest, upper back or the side of the chest. **BuTrans** should be applied to a relatively hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped, not shaven. Application should be rotated to a different area whenever a patch is replaced or added. **Application areas should be re-used at no less than 3-week intervals.** When returning to a previously used area, after at least 3 weeks, a different skin site should be used if possible. (See **PATIENT MEDICATION INFORMATION – Where to Apply BuTrans).**

If the application site must be cleaned, it should be done with clear water only. Soaps, alcohol, oils, lotions or abrasive devices must not be used. The skin site must be dry before the patch is applied. **BuTrans** should be immediately applied after removal from the sealed pouch.

Following removal of the protective layer, the transdermal patch should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure the contact is complete, especially around the edges. If the edges of the patch begin to peel off, the edge may be taped down with first aid tape. When applying the first aid tape, do not cover any printing on the **BuTrans** patch. Bathing, showering or swimming should not affect the patch. While wearing **BuTrans**, patients should be advised to avoid exposing the patch site to direct external heat sources (see **WARNINGS AND PRECAUTIONS**).

Dose Titration

Proper optimization of doses scaled to the relief of the individual's pain should aim at regular administration of the lowest dose of controlled release buprenorphine **(BuTrans)** which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects. On average, steady-state blood levels are achieved after 3 days. **It is recommended that doses of BuTrans be slowly titrated – with dosage adjustment generally separated by 7 days. The dose of BuTrans should not be increased before 3 days as the plasma concentrations continue to increase following application. Subsequent increases of BuTrans dosage must be individualized according to the pain relief and tolerance of the patient with adequate rescue medication, as required** (see **Management of Patients Requiring Rescue Medication**). If pain repeatedly occurs at the end of the dosing interval it is generally an indication for a dosage increase rather than more frequent administration of controlled release buprenorphine (**BuTrans**). Attempts should be made to identify the source of pain, while adjusting the **BuTrans** dose to decrease the level of pain. Dose adjustments may be made in 5 mcg/h or 10 mcg/h increments by using no more than two patches of the 5 mcg/h or 10 mcg/h system(s). **The total combined dose from all patches should not exceed 20 mcg/h**. Once a successful dose is determined, the patient should be given a prescription for a single patch of that dose.

To increase the dose, the patch that is currently being worn should be removed, disposed of properly, and the next higher strength of **BuTrans** should be used. Application sites should be rotated whenever a patch is replaced or added. Application areas should be re-used at no less than 3-week intervals. It is recommended that no more than two patches be applied at the same time. (See **PATIENT MEDICATION INFORMATION – How to Apply BuTrans**).

No change in dose titration is required in patients with renal impairment or mild to moderate hepatic impairment. Patients with severe hepatic impairment may accumulate buprenorphine and **BuTrans** should not be used in such patients.

Management of Patients Requiring Rescue Medication

During initiation, titration, and treatment with **BuTrans**, patients may continue their existing NSAID or acetaminophen regimen as needed. In clinical trials with **BuTrans**, acetaminophen and acetaminophen with codeine combinations were used as rescue medications. If episodes of pain are encountered with appropriate adjustments of the **BuTrans** dose, fentanyl products should not be used as rescue medication in patients taking **BuTrans**. Selection of rescue medication should be based on individual patient conditions. For patients whose dose has been titrated to the recommended maintenance dose, without attainment of adequate analgesia, the total daily dose may be increased, unless precluded by side effects.

If dose limiting adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated with appropriate medications such as laxatives or anti-nauseants. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

If adequate pain control cannot be achieved with the maximum patch dose of **BuTrans** 20 mcg/h every 7 days, the patient should be converted to an alternative around-the-clock μ-opioid agonist, and the dose of the alternative analgesic further titrated, as appropriate.

Managing Expected Opioid Adverse Experiences

Many patients receiving opioids, especially those who are opioid naïve, will experience side effects. Clinical trials have shown that these effects are most bothersome during the initial application and can be minimized by starting at **BuTrans 5** and gradually increasing the dose as needed. Although the side effects from **BuTrans** are often transient, some may require treatment. Adverse events such as constipation should be anticipated and treated with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Discontinuation of BuTrans Therapy

After removal of **BuTrans**, plasma concentrations decrease gradually, and the analgesic effect is maintained for a certain amount of time. This needs to be considered when use of **BuTrans** is to be followed by other opioids. As a general rule, a subsequent opioid should not be administered within 24 hours of removal of a **BuTrans** patch. As part of an overall strategy to suitably manage pain in this period, the use of appropriate rescue medication and/or careful monitoring during this time should be considered. Buprenorphine concentrations decline, decreasing approximately 50% in 12 hours (range 10-24 h). (See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**)

Safety and Handling

The buprenorphine contained in **BuTrans** is supplied in sealed transdermal patches. If the adhesive from the drug accidentally contacts the skin other than intended application site, the area should be washed with water. Do not use soap, alcohol or other solvents to remove the adhesive because they may enhance the absorption of the drug. When changing the patch, remove the used **BuTrans** patch, fold it over itself, and discard it (consult with a pharmacist about disposal options).

Disposal

BuTrans should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use. **BuTrans** should not be used in front of children, since they may copy these actions.

Upon removal, the used patch should be folded in half so that the adhesive side of the patch adheres to itself, and should be immediately packaged in such a way as to prevent accidental exposure to others, including children or pets until it can be returned to a pharmacy for proper disposal. If the drug adhesive layer-accidentally contacts the skin, the area should be washed with clear water. Used patches still contain a considerable amount of drug. Unused patches should be removed from their pouch, folded so that the adhesive side of the patch adheres to itself, and disposed of similarly to used patches. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacist for safe disposal.

BuTrans should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

OVERDOSAGE

For management of suspected drug overdose, contact your Regional Poison Control Centre.

Symptoms

The manifestations of **BuTrans®** (buprenorphine transdermal patch) overdose are an extension of its pharmacologic actions, but in overdose the antagonist properties may predominate. Symptoms include respiratory depression, sedation, drowsiness, nausea, vomiting and marked miosis. Respiratory depression has been absent in some cases of buprenorphine overdose. However, respiratory depression, including apnea, and cardiovascular collapse have occurred in other overdose situations.

Treatment

Support: Establish and maintain a patent airway, assist or control respiration as indicated, and maintain adequate body temperature and fluid balance. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

Topical Exposure: Remove any patch in contact with the patient and dispose of it properly.

Ingestion of BuTrans: Administer activated charcoal (either 1g/kg or 50 g) with an accompanying cathartic (e.g., 70% sorbitol, 1 mL/kg) to reduce buprenorphine absorption.

Opioid Antagonist: A specific opioid antagonist such as naloxone may reverse the effects of buprenorphine. The dose of naloxone required to antagonize the respiratory depressant effects of **BuTrans** may be in the range of 5 to 12 mg intravenously which is significantly higher than that

used for a narcotic such as morphine. The onset of naloxone effect may also be delayed by 30 minutes or more. Maintenance of adequate ventilation is essential when managing a **BuTrans** overdose and more important than specific antidote treatment with a narcotic antagonist, such as naloxone.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Buprenorphine is a lipophilic, partial agonist with potent activity at the μ-opioid receptor. Buprenorphine produces dose related analgesia up to doses of 1.0 mg subcutaneously. The exact mechanism of analgesia is not known, but it involves the binding to μ-opioid receptors in the central nervous system (CNS) and peripheral tissues. The drug may also alter the pain threshold (threshold of afferent nerve endings to noxious stimuli). Buprenorphine is highly lipophilic and binds with high affinity to μ-, κ-, and δ-opioid receptors. Buprenorphine binds and dissociates from the μ-receptor slowly, which may account for the prolonged duration of analgesia and, in part, for the limited physical dependence potential of the drug as well as explain why the administration of a narcotic antagonist (e.g., naloxone) does not readily reverse the respiratory depression, if it occurs.

Buprenorphine is also a kappa-receptor antagonist, but the clinical relevance of this finding has not been established. Like other opioid agonists, buprenorphine may produce increases in cerebrospinal fluid pressure, cause altered mentation, mental clouding or amnesia following intravenous administration.

Buprenorphine acts to reduce blood pressure in a manner similar to other opioids.

Opioids have been associated with effects on the neuraxis, resulting in alterations in plasma cortisol, growth hormone, and the immune system. The clinical significance of these opioid-induced changes in humans is unknown.

Like other opioids, buprenorphine may cause nausea, vomiting and constipation. Use of opioids may also result in an increase in biliary tract pressure as a result of spasm of the Sphincter of Oddi.

Buprenorphine causes dose-related miosis and produces urinary retention in some patients.

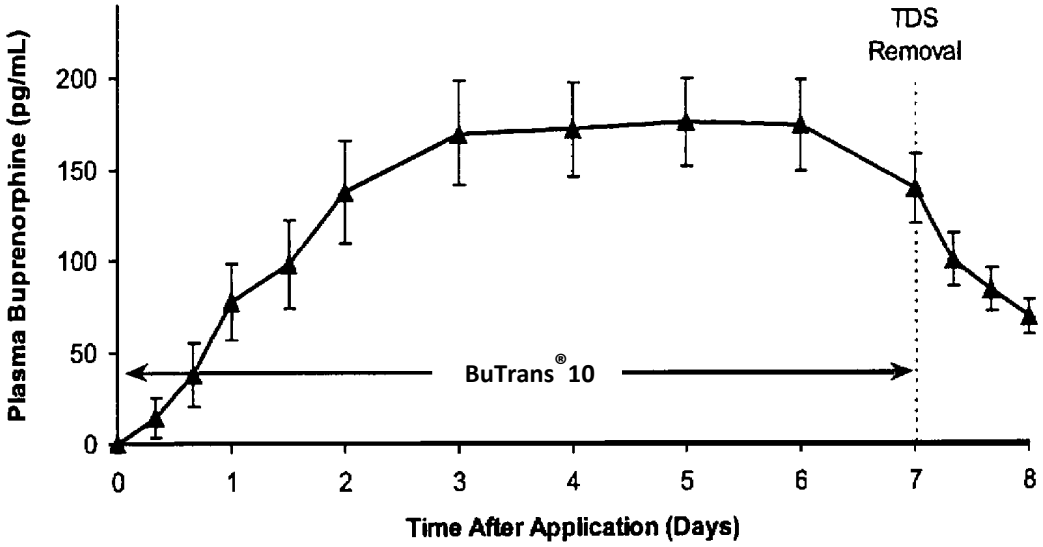
Pharmacokinetics

The composition of the four strengths of **BuTrans (5, 10, 15, 20)** is identical except for size. The amount of buprenorphine released from each patch per hour is proportional to the surface area of the patch. The skin is the limiting barrier to diffusion from the patch into the bloodstream. Flux rate through the skin was determined in two studies by three methods of analysis each yielding similar results. Buprenorphine flux for the 7 day application period was established to be 5, 10 and 20 mcg/h for the 7 day application period for the **BuTrans 5**, **10** and **20**, respectively.

Each **BuTrans** transdermal patch provides a steady delivery of buprenorphine for up to 7 days (see Figure 1). Steady state concentrations were achieved during the first application after day 3.

Figure 1: Buprenorphine Plasma Concentrations (pg/mL)

Mean (± 1.5 SEM), BuTrans®10 Application for 7 days
(N = 23 healthy subjects)



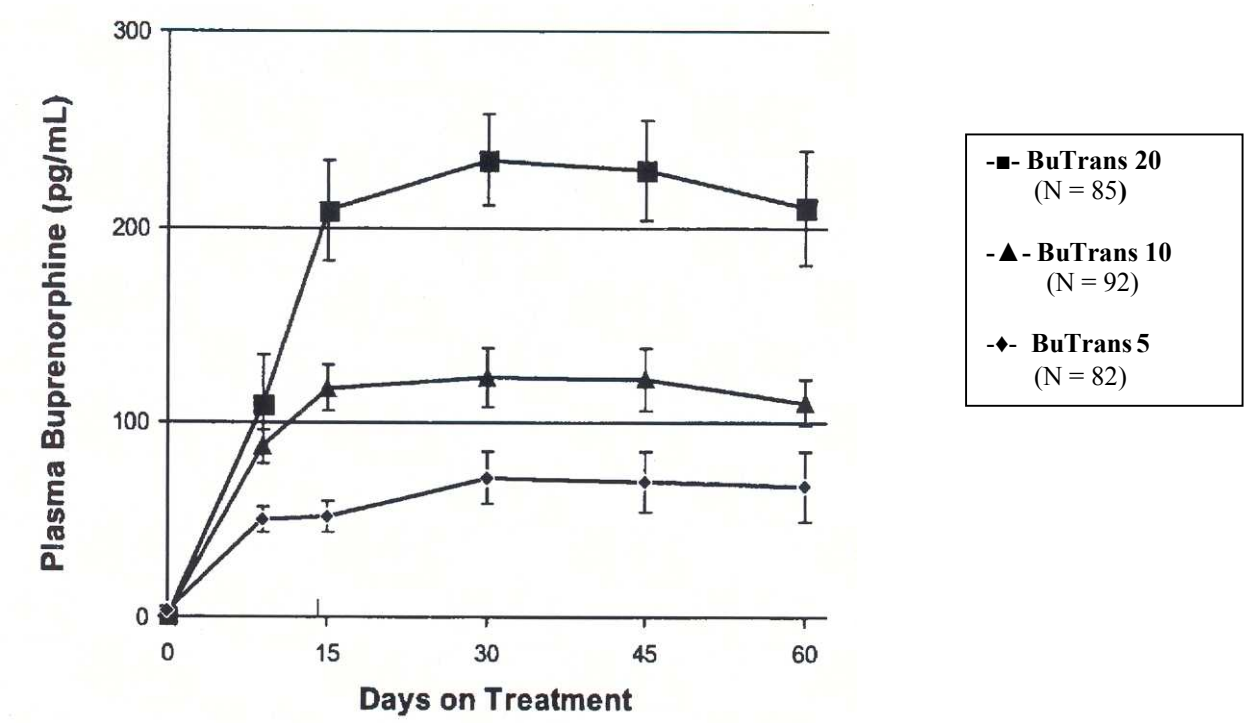
BuTrans 5, 10 and **20** provide dose-proportional increases in total exposure (AUC) over a 7 day application period (see Table 4). Dose-proportional increases in steady state plasma concentrations were maintained with **BuTrans** application for up to 60 days and accumulation of plasma buprenorphine did not occur (see Figure 2). After removal of **BuTrans**, buprenorphine concentrations decline, decreasing approximately 50% in 12 hours (range 10-24 h).

Table 4: Pharmacokinetic Metrics of BuTrans in Healthy Subjects (Single 7 day Application) Mean ± Standard Deviation

Dose	N	AUC (pg.h/mL)	Average Concentration (pg/mL)	C_{max} (pg/mL)
BuTrans 5	12	12,647 ± 2,015	75.3 ± 12.0	176 ± 34
BuTrans 10	12	24,311 ± 2,355	145 ± 14.0	191 ± 19
BuTrans 20	9	51,106 ± 6,156	304 ± 36.6	471 ± 77

Figure 2: Buprenorphine Plasma Concentrations (pg/mL)

Mean (± 1.5 SEM), 7 day wear of BuTrans 5, 10 or 20 for 60 days



Application Site: A study in healthy subjects demonstrated that the pharmacokinetic profile of buprenorphine delivered by **BuTrans** is similar when applied to the upper outer arm**,** upper chest, upper back or the side of the chest (midaxillary line, 5th intercostal space).

In a study of healthy subjects receiving **BuTrans** repeatedly to the same site, immediate reapplication caused increased absorption. For this reason, rotation of application sites is recommended.

In a study of healthy subjects, application of a heating pad directly on the **BuTrans** patch caused a transient, 26 - 55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed. For this reason, applying an external heat source directly, such as a heating pad, to the **BuTrans** patch during wear is not recommended. A heating pad applied to a **BuTrans** site, immediately after patch removal, did not alter absorption from the skin depot.

Absorption

Following **BuTrans** application, buprenorphine diffuses from the patch through the skin. In clinical pharmacology studies, the median time for **BuTrans 10** to deliver detectable buprenorphine concentrations (25 pg/mL) was approximately 17 hours. The absolute bioavailability of **BuTrans** relative to IV, following a 7 day application is approximately 15%

for all treatments (**BuTrans 5, 10, 20**). Plasma levels following sublingual buprenorphine doses of 4 mg to 16 mg have been reported to be in the range of 2000 – 4420 pg/mL. Plasma levels of oral sublingual buprenorphine are much higher in comparison to the plasma levels obtained in **BuTrans 20** patch administration (471 pg/mL).

Distribution

Buprenorphine is approximately 96% bound to plasma proteins. Studies of IV buprenorphine have shown a large volume of distribution, implying extensive distribution of buprenorphine. In a study of IV buprenorphine in healthy subjects, the volume of distribution at steady state was 430 L, reflecting the large volume of distribution and lipophilicity of the drug.

Following IV administration, buprenorphine and its metabolites are secreted into bile, and within several minutes, distribute into the cerebrospinal fluid (CSF). CSF buprenorphine concentrations appear to be approximately 15% to 25% of concurrent plasma concentrations.

Metabolism and Elimination

Buprenorphine metabolism in the skin following **BuTrans** application is negligible. Following transdermal application, buprenorphine is eliminated via hepatic metabolism, with subsequent biliary excretion and renal excretion of soluble metabolites. Hepatic metabolism, through CYP3A4 and UGT1A1/1A3 enzymes, results in two primary metabolites - norbuprenorphine and buprenorphine 3-O-glucuronide, respectively. Norbuprenorphine is also glucuronidated prior to elimination. Buprenorphine is also eliminated in the feces. Following intramuscular administration of 2 mcg/kg, approximately 70% of the dose was excreted in feces within 7 days. The total clearance of buprenorphine is approximately 55 L/h in postoperative patients.

Norbuprenorphine is the only known active metabolite of buprenorphine. It has been shown to be a respiratory depressant in rats, but only at concentrations at least 50 fold greater than observed following application of **BuTrans 20**.

Reductions in hepatic blood flow induced by some general anaesthetics (e.g., halothane) and other drugs may result in a decreased rate of hepatic elimination of the drug. Since buprenorphine elimination and metabolism is not solely dependent on the CYP450 enzyme system, inhibition of the CYP3A4 enzyme would not decrease buprenorphine clearance by non-CYP450 pathways, such as direct glucuronidation. **BuTrans** metabolism is not expected to be affected by the usual doses of drugs inhibiting CYP450 pathways. Based on in vitro studies in human microsomes and hepatocytes, buprenorphine does not appear to have the potential to inhibit metabolism by CYP450 isoenzymes at concentrations obtained with **BuTrans** use.

Endotoxin Challenge

In a crossover study of healthy subjects receiving endotoxin or placebo challenge during **BuTrans** wear, the AUC and C_{max} were similar despite a physiologic response to endotoxin. Therefore, **BuTrans'** performance is unlikely to be significantly affected during intercurrent mild febrile illness.

Special Populations and Conditions

Pediatrics: **BuTrans** has not been studied in children and is not indicated for patients less than 18 years of age.

Geriatrics: The pharmacokinetic profile of **BuTrans** is similar in healthy elderly and young adult subjects, although elderly subjects trended toward higher plasma concentrations of buprenorphine immediately after removal of **BuTrans**, than young adult subjects. Both groups eliminated buprenorphine at similar rates after patch removal.

Gender: No differences in plasma buprenorphine concentrations were detected between males and females treated with **BuTrans**.

Race: No data available.

Hepatic Insufficiency: In a pharmacokinetic study utilizing intravenous buprenorphine, there were no differences in clearance of buprenorphine between mild to moderate hepatically impaired subjects relative to healthy adult subjects. These data show no need for dosage adjustment when using **BuTrans** in patients with mild to moderate hepatic impairment.

Renal Insufficiency: Buprenorphine pharmacokinetics were similar in patients with severe renal impairment compared to normal adults (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Genetic Polymorphism: No data available.

Cardiovascular: In two thorough QTc studies, the effects of **BuTrans** on the QT interval were assessed in healthy volunteers. **BuTrans** 10 mcg/h was not different from placebo and was not associated with a clinically meaningful effect. **BuTrans** 20 mcg/h was not studied. **BuTrans** 40 mcg/h (not a recommended dose) was associated with a mean prolongation of the QT interval of 5.9 msec and 6.64 msec,compared to placebo.

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).

STORAGE AND STABILITY

Store at 15°C - 30°C.

Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

BuTrans® (buprenorphine transdermal patch) should be kept in a safe place out of the sight and reach of children before and after use. Do not give to others. **BuTrans** patches should not be divided, cut or damaged in any other way.

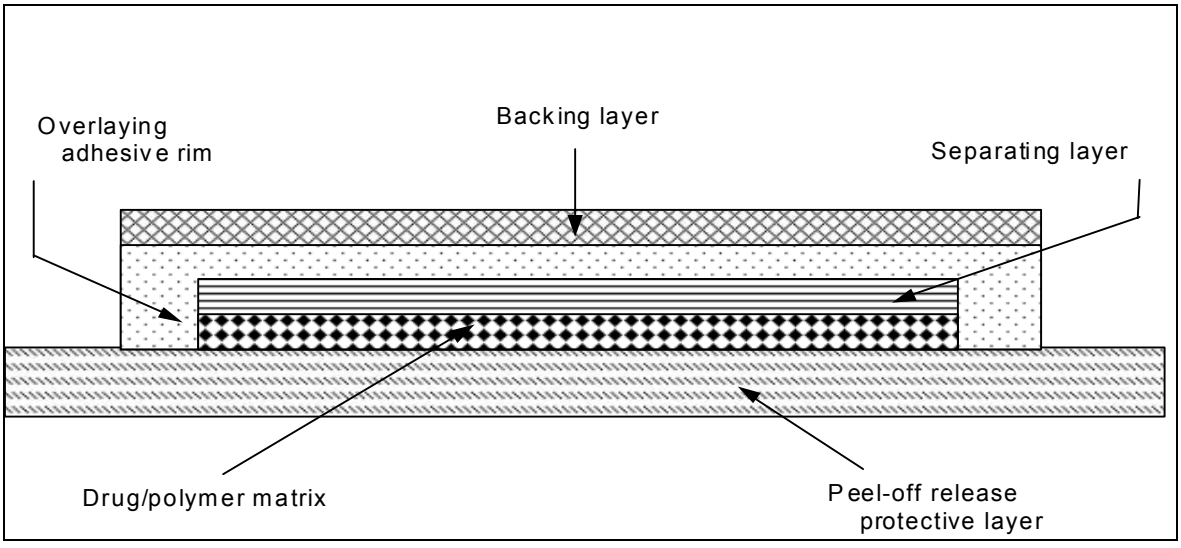
The buprenorphine contained in **BuTrans** is supplied in sealed transdermal patches. If the adhesive from the drug accidentally contacts the skin other than the intended application site, the area should be washed with water. Do not use soap, alcohol or other solvents to remove the adhesive because they may enhance the absorption of the drug. When changing the patch, remove the used **BuTrans**, fold it over itself, and discard it (consult with a pharmacist about disposal options).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Patch Components and Structure

BuTrans® (buprenorphine transdermal patch) is a rectangular or square, beige coloured patch consisting of a protective liner and functional layers. Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a beige coloured web backing layer of polyester material; (2) an adhesive matrix rim without buprenorphine; (3) a separating foil over the adhesive matrix; (4) the buprenorphine containing adhesive matrix with inactive ingredients including aluminum acetylacetonate, levulinic acid, oleyl oleate, polyacrylate (dry solids), povidone; and (5) a release liner (see Figure 3). Before use, the release liner covering the adhesive layer is removed and discarded.

Figure 3: Cross Section Diagram of BuTrans®



AVAILABILITY OF DOSAGE FORMS

Four strengths of **BuTrans**® (buprenorphine transdermal patch) are available: **BuTrans 5**, **BuTrans 10, BuTrans 15** and **BuTrans 20** (Table 5). The composition of all four strengths is identical except for size. The active component of the patch is buprenorphine. The remaining components are pharmacologically inactive. The amount of buprenorphine base mixed in the adhesive matrix is the same for each of the strengths (10% by weight). The amount of buprenorphine released from each patch per hour is proportional to the surface area of the patch.

Table 5: BuTrans Product Specifications - Delivery Rate and Active Surface Area

Total Buprenorphine Content (mg)	Delivery Rate (mcg/h)	Active Surface Area (cm^2)
BuTrans 5	5	6.25
BuTrans 10	10	12.5
BuTrans 15	15	18.75
BuTrans 20	20	25.0

BuTrans 5, 10, 15 and **20** Transdermal Patches are available in cartons of four (4) patches.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

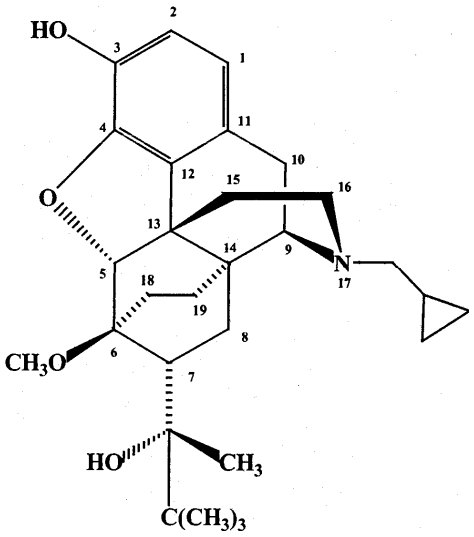
Drug Substance

Proper Name: Buprenorphine

Chemical Name: 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy- α -methyl-6, 14-ethenomorphinan-7methanol-, [5 α, 7 α, (S)]

Molecular Formula and Molecular Mass: $C_{29}H_{41}NO_4$, 467.6 g/mole

Figure 4: Structural Formula:



Physicochemical Properties: Buprenorphine is an opioid analgesic. White or almost white crystalline powder. Very slightly soluble in water. Freely soluble in acetone. Soluble in methanol, ethanol and diethyl ether. Slightly soluble in cyclohexane.

CLINICAL TRIALS

The safety and efficacy of **BuTrans®** (buprenorphine transdermal patch) has been evaluated in five pivotal clinical trials n = 797 patients treated with **BuTrans** for the management of two types of persistent pain, osteoarthritis and low back pain.

Pivotal Study Demographics and Trial Design

Table 6: Summary of Study Design and Demographics for Clinical Trials in Chronic Pain

Study #	Trial design (All trials are randomized, double-blind, double-dummy)	Dosage, route of administration, and duration of double-blind period	Number of Randomized Patients (by treatment)	Mean age (Range)	Primary Efficacy Variable
Study 1 (BP96-0604)	Placebo-controlled 3-arm, parallel design, titration-to-effect, in patients[a] with chronic back pain: Patients were randomized to **BuTrans** vs. Oxycodone/ acetaminophen tablets vs. Placebo	**BuTrans** 5, 10 or 20 mcg/h transdermal patch vs. 5 mg oxycodone/325 mg acetaminophen tablets (qid) vs. Placebo Duration: 12 weeks	N = 134 total **BuTrans**-46 Oxycodone/acetaminophen–43 Placebo-45	52 (19-85)	Pain on average (0-10) Pain right now (0-10) Assessment with repeated measures analysis (multiple time points)for double-blind phase
Study 2 (020-007)	Placebo-controlled, 2-way crossover, titration-to-effect design: Patients with chronic back pain were randomized to **BuTrans** vs. placebo	**BuTrans** 10, 20 or 40 (2x20) mcg/h transdermal patch(es) vs. Placebo Supplemental pain meds: PRN acetaminophen 325mg, max. 12 tablets/day Duration: 8 weeks (4 weeks/phase)	N = 78 total **BuTrans**-73 Placebo-68	51 (27-77)	Pain Intensity (100mm VAS and Ordinal Scale 0-4) in the last week of treatment in each phase

Table 6: Summary of Study Design and Demographics for Clinical Trials in Chronic Pain

Study #	Trial design (All trials are randomized, double-blind, double-dummy)	Dosage, route of administration, and duration of double-blind period	Number of Randomized Patients (by treatment)	Mean age (Range)	Primary Efficacy Variable
Study 3 (020-006)	Placebo-controlled, 2-way crossover, titration-to-effect design: Patients with chronic back pain were randomized to **BuTrans** vs. placebo	**BuTrans 5, 10** or **20** mcg/h transdermal patch vs. Placebo Supplemental pain meds: PRN codeine 30 mg/ acetaminophen 300 mg, max. 12 tablets/day Duration: 8 weeks (4 weeks/phase)	N = 79 total **BuTrans**-73 Placebo-68	54 (20-76)	Pain Intensity (100mm VAS and Ordinal Scale 0-4) in the last week of treatment in each phase
Study 4 (BUP3015)	Active control, 3-arm parallel design, in patients with chronic back pain: After 3 weeks open-label exposure to **BuTrans**, patients were randomized to **BuTrans** 5 or 20, or immediate-release oxycodone	**BuTrans** 5 mcg/h transdermal patch vs. **BuTrans** 20 mcg/h, transdermal patch vs. IR oral oxycodone 40 mg/day Supplemental pain meds: PRN acetaminophen 500mg, max. 4g/day or PRN ibuprofen 200mg, max. 3,200mg/day Duration: 12 weeks	N = 660 total **BuTrans 5**-221 **BuTrans 20**-219 Oxy•IR-220	50 (21-89)	Average pain over the last 24 hours (0-10) Assessment with repeated measures analysis (multiple time points) for double-blind phase
Study 5 (BUP3012)	Placebo-controlled, 2-arm parallel design, maintenance of analgesia in patients[b] with osteoarthritis of the hip or knee: After 3 weeks stabilization on **BuTrans**, patients were randomized to **BuTrans** vs. Placebo	**BuTrans** 5, 10 or 20 mcg/h transdermal patch vs. Placebo Supple pain meds: acetaminophen 500 mg PRN, max. 8 tablets/ day Duration: 4 weeks	N = 327 total **BuTrans**-165 Placebo-162	61 (36-79)	Time to development of inadequate analgesia (For criteria, refer to Study 5 description)

a. Approximately 80% of patients were opoid naïve

b. Approximately 98% of patients were opioid naïve

Study 1 (BP96-0604)

A 12 week double-blind, double-dummy, 3-arm parallel-design, placebo-controlled, titration-to-effect study was conducted in 134 patients with chronic back pain. Approximately 80% of the patients were opioid naïve. Patients were randomized 1:1:1 to receive **BuTrans (**5, 10 or 20 mcg/hr), or 5 mg oxycodone/325 mg acetaminophen tablets (1-3 tablets QID), or placebo. Patients were initiated on the lowest dose and titrated during the first 3 weeks to achieve acceptable analgesia. The primary efficacy measures were "Average pain over the last 24 hours" (0-10 scale), and "Pain right now" (0-10 scale). The primary efficacy endpoint was mean change from baseline for the maintenance period (Day 21 to Day 84; six scheduled assessment points), as determined by repeated measures analysis of variance. The primary comparison was **BuTrans** vs placebo.

The difference between the **BuTrans** and placebo groups was significant for both "pain on average" (-1.92 ± 0.34 vs. -1.01 ± 0.37, respectively, p = 0.035), and "pain right now" (-1.66 ± 0.34 vs. -0.80 ± 0.38, respectively, p = 0.045).

Studies 2 and 3 (020-007, 020-006)

Both studies were randomized, double-blind, double-dummy two-way crossover studies comparing **BuTrans** and placebo over a 4 week period per phase in patients with chronic low back pain (n= 78 and 79 patients, respectively). In both studies, the primary measure of efficacy was pain intensity (100 mm VAS and 0-4 ordinal) measured over the last week of treatment in each phase.

In Study 2, patients were titrated to effect in each phase, using 10, 20 or 40 mcg/h doses (**BuTrans** or placebo). Acetaminophen 325 mg tablets were provided in both phases for rescue analgesia (1-2 tablets prn, maximum 12 tablets/day). **In Study 3**, patients were titrated to effect in each phase, using 5, 10 or 20 mcg/h **BuTrans** or placebo. Codeine 30 mg/acetaminophen 300 mg tablets were provided for rescue analgesia in both phases (1-2 tablets prn, maximum 12 tablets/day).

As shown in Table 7 and Table 8, the pain intensity scores during the last week of treatment were significantly lower with **BuTrans** than with placebo for both primary endpoints, in both studies. While no carryover effect was detected, the treatment difference in pain intensity scores between active and placebo arms was greater in the second phase for both crossover studies.

Table 7: Study 2 (020-007)

Primary Endpoints	**Associated ~~v~~Values and Statistical ~~s~~Significance**
Pain Intensity (100mm VAS), Last Week of Treatment	Baseline 60.9 ± 15.4 **BuTrans** **Placebo** (plus PRN acetaminophen) 45.3 ± 21.3 53.1 ± 24.3 p = 0.0219

Table 7: Study 2 (020-007)

Primary Endpoints	Associated ~~v~~Values and Statistical ~~s~~Significance
Pain Intensity (Ordinal Scale, 0-4), Last Week of Treatment	Baseline 2.6 ± 0.5 **BuTrans** **Placebo** (plus PRN acetaminophen) 1.9 ± 0.7 2.2 ± 0.8 p = 0.0439

Table 8: Study 3 (020-006)

Primary Endpoints	Associated ~~v~~Values and Statistical ~~s~~Significance
Pain Intensity (100mm VAS) – Last Week of Treatment	Baseline 62.1 ± 15.5 **BuTrans** **Placebo** **(**plus PRN codeine 30mg/acetaminophen) 37.6 ± 20.7 43.6 ± 21.2 p = 0.0487
Pain Intensity (Ordinal Scale 0-4) – Last Week of Treatment	Baseline 2.5 ± 0.6 **BuTrans** **Placebo** **(**plus PRN codeine 30mg/acetaminophen) 1.7 ± 0.6 2.0 ± 0.7 p = 0.0358

Study 4 (BUP3015)

A 12 week double-blind, double-dummy parallel-design, 3-arm active-control study was conducted in 660 patients with chronic back pain randomized 1:1:1 to receive **BuTrans 5,** or **BuTrans 20,** or immediate release oxycodone (Oxy·IR). Each patient entering the 12-week double-blind phase had demonstrated analgesic benefit and tolerability with **BuTrans 20** treatment in the 3 week open-label run-in period. The primary measure of efficacy was "Average pain over the last 24 hours" (0-10 scale). The primary efficacy endpoint was mean pain measurement scores for Weeks 4, 8 and 12, as determined by repeated measure analysis of variance. The primary comparison was **BuTrans 20** vs **BuTrans 5.** The difference in pain scores for these two strengths was assessed using the least square means at weeks 4, 8 and 12 estimated from the mixed effects linear model.

Patients randomized to **BuTrans 20** had statistically significantly lower mean pain scores than those randomized to **BuTrans 5** (difference of 0.67, $p < 0.001$).

Study 5 (BUP3012)

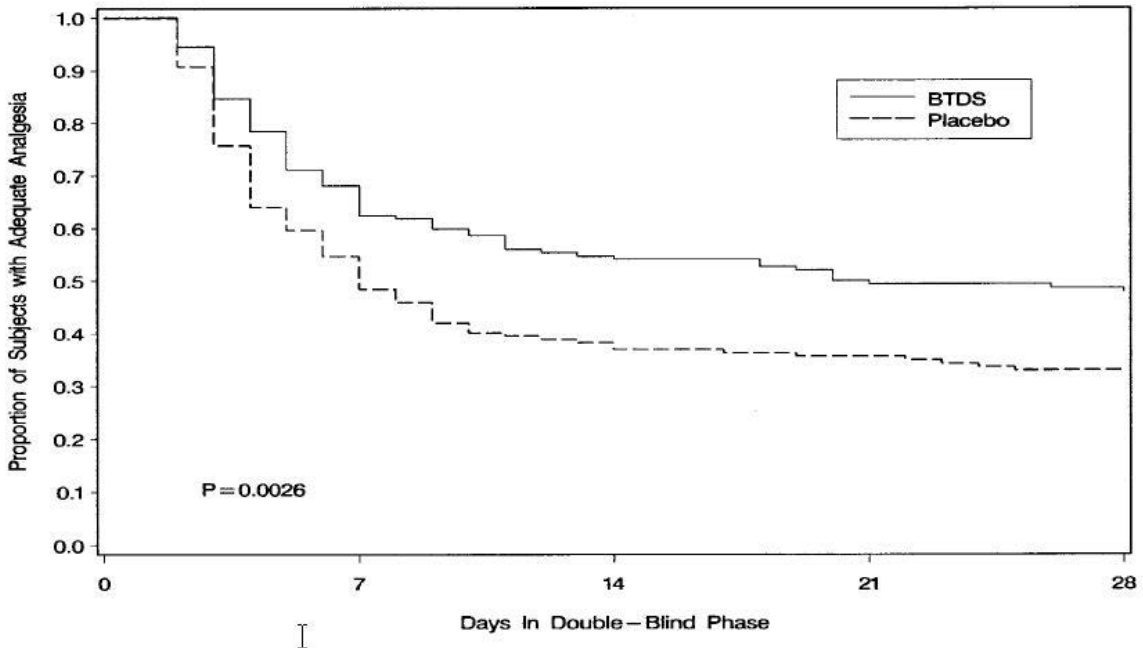
A 4-week "maintenance of analgesia", double-dummy, 2-arm, parallel-design placebo-controlled study was conducted in patients with chronic pain due to osteoarthritis (OA) of the hip or knee. Patients were first screened into a maximum 3-week open-label run-in period, and those who achieved the criteria of adequate analgesia while on the same patch (5, 10 or 20 mcg/h dose) for 7 consecutive days were randomized 1:1 to receive **BuTrans** or placebo (n= 529 patients screened in; n = 327 patient randomized). Assigned dose in the double blind period for each patient was the individual dose achieved in the open-label period. Approximately 98% of the n = 529 patients were opioid naïve.

The primary efficacy endpoint was time (days) from the initial double-blind dose to the onset of inadequate analgesia, defined as:

1) Patient's pain over the last 24 hours for primary OA site was ≥ 5 (11-point scale) on any 2 days or more, or
2) Patient required >1000 mg/day acetaminophen for pain at primary OA site for 2 days or more, or
3) The first day the patient required another opioid for pain at primary OA site.

The proportion of patients who completed the double-blind period (i.e., reached either the primary endpoint of inadequate analgesia or the 4-week time point) was not different between the treatment arms (93% for **BuTrans** and 97% for placebo). A total of three patients, all in the placebo arm, reported the onset of one or more symptoms of opioid withdrawal during the double-blind phase. None of the patients transferring from active treatment to placebo were considered to have experienced opioid withdrawal based on investigator assessment, in the context of protocol specified criteria for "definite withdrawal". Of the patients who completed, 54% (83 /153) in the **BuTrans** arm developed inadequate analgesia compared to 68% (107 /157) in the placebo arm. The median time to onset of inadequate analgesia was significantly longer for subjects receiving **BuTrans** than for subjects receiving placebo. (**BuTrans** = 21 days vs. placebo = 7 days; p=0.0026 based on log-rank statistic). The treatment difference between the placebo group and the **BuTrans** group was maintained for the 4-week duration.

Figure 5: Kaplan-Meier Survival Plot for the Time (Days) to Onset of Inadequate Analgesia at the Primary OA Pain Site



DETAILED PHARMACOLOGY

Buprenorphine is a lipophilic, partial agonist, semi-synthetic narcotic opioid of the oripavine series. Buprenorphine acts as a partial agonist at the μ-receptors and as a kappa (κ) antagonist. Buprenorphine also binds to the orphanin (nociceptin) receptor where it is a full agonist.

Buprenorphine binds to opiate receptors with a stronger potency than morphine. In a binding study using human recombinant receptors, buprenorphine had a K_I of 1.33 nM at the μ receptor as compared to a published K_I of 230 nM for morphine, showing a >100 fold relative potency. Buprenorphine also binds to the κ receptor with a K_I of 0.157 nM, to the δ receptor with a K_I of 1.9 nM, and to the orphanin (nociceptin) receptor with a K_I of 128 nM. Buprenorphine acts as a partial agonist, consistent with molecular studies that show only 66% of full agonist activity to increase [^{35}S]GTP$_y$S binding. Buprenorphine is hypothesized to dissociate slowly from its receptor once bound (pretreatment with a narcotic antagonist can prevent pharmacologic effects, but once established, effects are not readily reversible by administration of a narcotic antagonist). In most studies in vivo, buprenorphine is 10 to 100 fold more potent than morphine, in line with buprenorphine's relative binding potency at the μ receptor. Pharmacologic effects observed following buprenorphine administration are consistent with known opioid pharmacology.

Animal studies have demonstrated a blunting of the dose response curve for respiratory effects with buprenorphine. The relevance of this effect at analgesic doses in man is unknown.

Endocrine System

Opioids may also influence the hypothalamic –pituitary-adrenal or –gonadal axes, including an increase in serum prolactin an decreases in plasma cortisol and testosterone, which can manifest in clinical symptoms.

Other Pharmacological Effects

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether buprenorphine, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

In vitro data suggests that buprenorphine is a human cardiac HERG potassium channel inhibitor, although at concentrations higher than used clinically. The clinical significance of this finding is unknown.

TOXICOLOGY

Acute Toxicity

The acute toxicity of buprenorphine is dependent on the route of administration. Acute toxic signs associated with buprenorphine administration are similar to those of other opioids and consist of convulsions and changes in motor activity including ataxia. Cause of death is attributed to cardiorespiratory failure. LD_{50} values in the mouse and rat range from 24 to 72 mg/kg and 31 to 62 mg/kg, respectively following intravenous (IV) administration and are >1,000 mg/kg in both species following subcutaneous (SC) administration. The values following subcutaneous administration (the closest approximation to dermal application of a patch) showed the LD_{50} in mice and rats is approximately 3400 times the projected human dose on a mg/kg basis (assuming the worst case scenario of complete and immediate release of all material in the patch).

Long-term Toxicity and Carcinogenicity

No mortality or organ toxicity was seen in 90-day toxicity studies in rats and dogs at doses up to 5 and 2.5 mg/kg, respectively (approximately 50 and 25 times the human dose, respectively).

Studies conducted using dermal application of the Buprenorphine Transdermal Patch for up to 6 months have been conducted in rabbits, dogs and minipigs. No drug related mortality or organ toxicity was seen.

Buprenorphine was administered by skin painting to Sprague-Dawley rats for 100 weeks at dosages (0, 20, 60, and 200 mg/kg/day) that produced systemic exposures (based on AUC) that range from 88- to 342- times that of human subjects administered **BuTrans**® (buprenorphine transdermal patch) 20mcg/h. Statistically significant increased incidences of three tumour types (benign testicular interstitial cell tumours in mid and high dose male rats, benign adrenal medullary pheochromocytomas in female rats at all dose levels, and endometrial stromal benign

polyps/malignant sarcoma in female rats at the low and high dose levels were considered to be buprenorphine-related. The increased incidences were at or slightly above the highest incidences in the historical control database of testing facility, except for the endometrial polyp/sarcoma incidence at the low dose level that was within the historical control range. The occurrence of these tumours at high dose levels in rats are considered of low relevance to humans, based on the relatively high sensitivity of the rat to these tumour types, and the high exposure margins achieved relative to humans using the **BuTrans** 20 mcg/h product. Furthermore, the increased incidences of adrenal medullary and endometrial (including a stromal sarcoma) tumours were not dose-dependent. The mechanism(s) leading to the tumour findings are unknown.

Buprenorphine was administered by skin painting to hemizygous Tg.AC transgenic mice over a 6-month study period. At the dosages administered (0, 18.75, 37.5, 150, and 600 mg/kg/day), systemic exposure (AUC) to buprenorphine ranged from about 50- to 440 times that of human subjects administered **BuTrans** 20mcg/h. Buprenorphine was not tumourigenic in the study.

Mutagenicity

Buprenorphine was not genotoxic in 4 genetic toxicology studies (bacterial mutagenicity test, mouse lymphoma assay, chromosomal aberration assay in human peripheral blood lymphocytes, and an in vivo mouse micronucleus test).

Reproduction and Teratology Studies

Impairment of fertility: **BuTrans** or subcutaneous administration of buprenorphine had no effect on fertility or general reproductive performance of rats at exposure levels (AUC) as high as 100- to 152- times that of human subjects who received **BuTrans** 20 mcg/h.

Reproductive toxicity studies showed that buprenorphine was not teratogenic and had no effect on reproductive capacity, duration of gestation or parturition. An increase in fetal deaths and increased pup mortality was seen, indicating buprenorphine may have mild embryocidal properties in rodents. There is some indication that buprenorphine may affect milk production, which could be related to pup mortality. The relevance to human pregnancy is unclear.

Tissue Irritation and Administration Studies

Buprenorphine did not cause dermal sensitization in guinea pigs. Other safety/special toxicity studies showed that no significant toxicity was observed in dogs following buccal or oral administration of the buprenorphine transdermal patch (to mimic swallowing/ mouthing a buprenorphine transdermal patch). Following buccal administration a mean C_{max} that was approximately 370 times the C_{max} seen in man (following application of a 20 mcg/h buprenorphine transdermal patch for 7 days) was observed. No significant effect on plasma concentrations in minipigs was seen following immersion in a heated bath.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^{N}BuTrans®
Buprenorphine Transdermal Patch

Read this carefully before you start taking **BuTrans** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BuTrans**.

Serious Warnings and Precautions

- **Even if you take BuTrans as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., doctor).**
- **Life-threatening breathing problems can happen while taking BuTrans, especially if not taken as directed.**
- **Never give anyone your BuTrans. They could die from taking it. Touching the medicated side of a patch can cause a fatal overdose to people who have not been prescribed this medication, especially children. Avoid accidental contact between the patch and other people, especially when holding or caring for children.**
- **Babies born to mothers who have taken BuTrans (for short or long periods, in small or large doses) during their pregnancy can suffer life-threatening withdrawal symptoms. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has breathing changes (weak, difficult or fast), is unusually difficult to comfort, has tremors (shakiness), or has increased stools, sneezing, yawning, vomiting, or fever, seek immediate medical help for your baby.**

What is BuTrans used for?

BuTrans is used for the long-term management of pain, when:

- the pain is severe enough to require daily, around-the-clock pain medication
- the doctor determines that other treatment options are not able to effectively manage your pain

BuTrans is NOT used ("as needed") to treat pain that you only have once in a while.

How does BuTrans work?

BuTrans contains buprenorphine which is a pain medication belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in BuTrans?

Medicinal ingredient:	buprenorphine
Non-medicinal ingredients:	Protective liner: polyethylene terephthalate Backing layer: polyethylene terephthalate Drug in adhesive layer: aluminum acetylacetonate, levulinic acid, oleyl oleate, polyacrylate (dry solids) and povidone

BuTrans comes in the following dosage forms:

Transdermal patches 5 mg, 10 mg, 15 mg and 20 mg buprenorphine per patch, delivering 5 mcg, 10 mcg, 15 mcg and 20 mcg buprenorphine per hour, respectively, for 7 days.

Do not use BuTrans if:

- you are allergic to buprenorphine, other opioids, or any of the other ingredient in the formulation or component of the container of **BuTrans**
- your pain can be controlled by the occasional use of pain medication including those available without a prescription
- you have severe asthma, trouble breathing, or any heart problems
- you have bowel blockage or narrowing of the stomach or intestines (e.g., paralytic ileus)
- you have severe pain in your abdomen
- you have a head injury or other risks for seizures
- you suffer from alcoholism
- you are being treated for narcotic withdrawal
- you are pregnant or plan to become pregnant, breast-feeding, or in labour
- you have myasthenia gravis
- you have severe liver disease
- you are under 18 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take **BuTrans**. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney disease
- have low blood pressure
- are going to have, or recently had, a planned surgery

- have past or current depression
- have problems with your thyroid, adrenal or prostate gland
- suffer from chronic or severe constipation

Other warnings you should know about:

Do not expose the patch area to sources of heat such as heating pads, electric blankets, heated waterbeds, heat lamps, saunas and hot tubs, intensive sunbathing, etc. This may increase the drug's ability to go through the skin and result in an overdose. This may also occur if you develop a fever.

There are important differences between physical dependence and addiction, and each is a reason for close medical supervision and honest discussions with your doctor. If you have questions or concerns about abuse, addiction or physical dependence, please tell your doctor.

Driving and using machines:

Before you perform tasks which may require special attention, wait until you know how you respond to **BuTrans**. Drowsiness, dizziness, or lightheadedness, can especially occur after the first dose and when the dose is increased.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BuTrans:

- alcohol, including prescription and non-prescription medications containing alcohol. Do not drink alcohol while taking **BuTrans**. This can lead to drowsiness, depressed breathing, serious side effects or a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by **BuTrans**
- other opioid analgesics (for pain)
- general anesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety
- antidepressants (for depression and mood disorders). Do not take **BuTrans** with monoamine oxidase (MAO) inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with **BuTrans**
- drugs used to treat serious mental or emotional disorders, such as schizophrenia
- antihistamines (for allergies)
- anti-emetics (for prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots)
- anti-retroviral, anti-fungal and antibiotic drugs
- grapefruit juice

How to use BuTrans:

BuTrans an adhesive, rectangular or square patch that is placed on your skin. The patch slowly releases buprenorphine over a period of 7 days.

BuTrans should only be used on the skin.

- always remove the old patch before applying a new one. This is important to avoid overdose.
- apply on clean, dry, intact, non-hairy area on your upper chest, upper back, or upper arm. If the area you choose has body hair, clip (do not shave) the hair close to the skin with scissors.
- if you need to clean the skin where the patch will be applied, use only clear water.

Do not:

- apply heat to the area before or after applying the patch.
- chew, swallow, put it in your mouth, or use the patch in any way other than on the skin.
- wear more than one patch at a time, unless your doctor tells you to.
- use the **BuTrans** patch if the seal is broken or the patch is cut, damaged or changed in any way.
- apply your patch in front of children since they may copy your actions.

You can bathe, swim, or shower while wearing **BuTrans**. If the patch falls off, discard the patch properly. Apply a new patch at a different skin site. Make sure the new skin area is dry. Tell your doctor that this has happened. Take note of the time you applied the new patch and change it only after the required number of hours.

Where to Apply BuTrans:

Select a dry, hairless or nearly hairless **area**, on your upper chest (left or right), upper back (left or right) side of chest (left or right) or upper outer arm (left or right) (**see Figure A**).

Application Areas

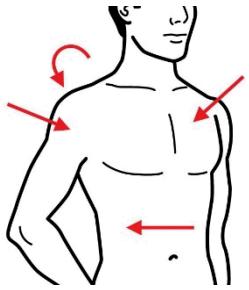

Figure A

Within each of the application **AREAS** there is more than one possible **SITE** for applying the patch.

Possible application **SITES** in upper chest areas (left or right) (**see Figure B**), or the upper back areas (left or right) (**see Figure C**) or the right side of the chest and upper arm (**see Figure D**) or the left side of the chest and upper arm (**see Figure E**).

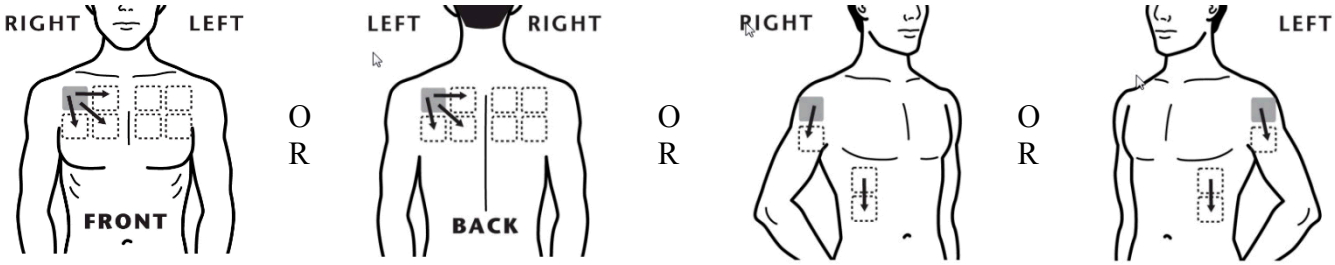

Figure B **Figure C** **Figure D** **Figure E**

Do not apply more than one patch at the same time unless prescribed by your doctor.

If your doctor tells you to use two patches make sure you apply **both** patches at the same time and at the same site right next to each other (**see Figure F**). Make sure you always:

- apply **both** patches at the same time
- remove **both** patches at the same time

Do not use more than a total **combined** dose from all patches of 20 mcg per hour.

Figure F

If the area (site) you choose has body hair, **do not** shave the hair. Clip the hair close to the skin with scissors (**see Figure G**).

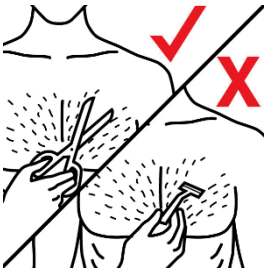

Figure G

Do not put the patch on skin that is excessively oily, burned, broken out, cut, irritated or damaged in any way. If you need to clean the skin where the patch will be applied, use only clear water. Soaps, oils, lotions, alcohol or other products may irritate the skin under the patch.

How to Apply BuTrans:

Step 1 - Each patch is sealed in its own protective pouch. Do not remove the patch from the pouch until you are ready to use it. When you are ready, remove the patch from the pouch.

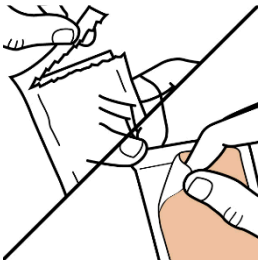

Figure H

Step 2 - A protective liner covers the sticky side of the patch – the side that will be put on your skin. Remove the thin section of liner located at one side of the patch and apply the thin sticky side of the patch to a dry area of your upper chest, upper back, side of chest, or upper outer arm (see **Figure H**).

Step 3 - Remove the remainder of the liner and immediately press the patch firmly on your skin with the palm of your hands for about 30 seconds. Try not to touch the sticky side of the patch. Throw away the liner (see **Figure I**).

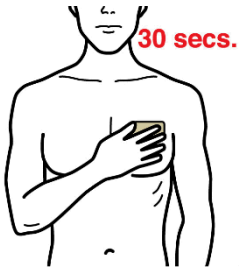

Figure I

Not all adhesive products stick to all patients. If an edge of the patch does not stick well, or loosens after application, tape the edges down with first aid tape. When applying the first aid tape, do not cover any printing on the **BuTrans** patch. In the event that the patch falls off, discard it and put a new one on at a different skin site. If two patches were applied at the same time and one falls off, remove the second patch from the body. Throw both of these patches away. Apply two **new** patches next to each other on a different skin site (see **Disposal** instrutions below).

Step 4 - Wash your hands, with water, when you have finished applying the patch.

Step 5 - After wearing the patch for 7 days, or as directed by your doctor, remove it (see **Disposal** instrutions below). Then choose a different area (to apply a new patch and repeat steps 1 to 4 in order. The same area should not be re-used within 3 weeks. This will reduce the possibility of developing a rash. After 3 weeks when returning to a previously used area, vary the skin sites if possible.

Contact your doctor or pharmacist if you have any questions about applying **BuTrans.**

Safety and Handling:

BuTrans is sealed to keep the drug adhesive layer from getting on your hands or body. If the drug adhesive layer accidentally touches the skin, wash the area with large amounts of water. Do not use soap, alcohol, or other solvents as these may increase the drug's ability to go through the skin.

Serious medical consequences, including death, can occur when patches are accidentally transferred to other people during skin-to-skin contact, for example while hugging, sharing a bed or moving a patient. If your patch dislodges and accidentally sticks to the skin of another person, take the patch off the other person immediately and call a doctor. This is true for both fresh and used patches, as there is drug that remains in the patch after use.

Usual Adult Starting Dose:

Dosage is individualized. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Because the medicine in **BuTrans** is gradually released from the patch, and slowly absorbed through the skin, do not expect immediate relief after you apply your first patch. During this initial period, your doctor may ask you to take additional pain medicine until you experience the full benefits of **BuTrans**.

Be aware that removing the patch does not completely remove the source of drug, as drug is deposited under the skin and will continue to be released into the bloodstream, although briefly, after patch removal.

If you continue to have pain, call your doctor.

Overdose:

Signs of overdose may include abnormally slow or weak breathing, dizziness, confusion or extreme drowsiness. Other signs of buprenorphine overdose may include tiredness, nausea, vomiting and constriction of the pupils.

If a person is having the above signs of overdose, check all areas of their skin and remove any patches. There may be more than one patch, if a previous patch was not removed. Get immediate emergency medical help.

If you think you have taken too much **BuTrans**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If a patch is left on for more than 7 days, remove the patch and apply a new patch following the instructions given (see **Where to Apply BuTrans** and **How to Apply BuTrans**).

Discontinuation:

Please do not suddenly stop taking **BuTran**s as it may cause unwanted side effects. Your doctor can instruct you as to the best way for you to stop taking **BuTrans**.

Refilling Prescriptions for BuTrans:

A new written prescription is required from your doctor each time you need more **BuTrans**. Therefore, it is important that you contact your doctor before your current supply runs out.

What are possible side effects from using BuTrans?

These are not all the possible side effects you may feel when taking **BuTrans**. These effects may be more pronounced if you have a fever. If you experience any side effects not listed here, or develop a fever while using the patch, contact your healthcare professional.

Side effects may include:

- application site reactions (e.g., itching, redness and/or rash)
- anorexia
- constipation
- dizziness
- drowsiness, insomnia
- dry mouth
- headache
- lack of muscle strength
- nausea, vomiting
- sweating

Talk with your doctor or pharmacist about ways to prevent constipation when you start using **BuTrans**.

Opioid withdrawal symptoms such as nausea, vomiting, diarrhea, anxiety and shivering are possible when converting from your previous opioid analgesic to treatment with **BuTrans**. Contact your doctor if you experience these symptoms when switching to or from **BuTrans**.

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Rare	**Overdose:** Hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
	Respiratory Depression: Slow, shallow or weak breathing.			√
	Allergic Reaction: Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			√
	Bowel Blockage (impaction): Abdominal pain, severe constipation, nausea.			√
	Fast, Slow or Irregular Heartbeat: Heart palpitations.		√	
	Low Blood Pressure: Dizziness, fainting, light-headedness.	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep unused, used, or expired **BuTrans** in a secure place to prevent theft, misuse or accidental exposure.

Store **BuTrans** between 15°C and 30 °C. Do not freeze.

Keep **BuTrans** in its protective pouch until you are ready to use it.

Remember, the inside of your car can reach temperatures much higher than 30°C on a sunny day. Do not carry the pouch in your pocket as it may reach body temperature (36°C).

Keep BuTrans under lock and out of sight and reach of children and pets. If a child accidentally comes in contact with BuTrans, get emergency help right away.

Disposal:

Remove the patch you have been wearing, before putting on a new **BuTrans** patch. Fold the used patch in half so the sticky side sticks to itself. If the drug adhesive layer accidentally contacts the skin, the area should be washed with clear water.

Wash your hands, with water only, after removing the patch.

BuTrans should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about BuTrans:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website; the manufacturer's website http://www.purdue.ca, or by calling 1-800-387-4501.

This leaflet was prepared by Purdue Pharma.

Last Revised: August 5, 2016

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