BUPRENORPHINE- buprenorphine patch, extended release
Praxis, LLC

BUPRENORPHINE transdermal system, CIII

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Buprenorphine transdermal system contains buprenorphine, a Schedule III controlled substance.

9.2 Abuse

Buprenorphine transdermal system contains buprenorphine, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.1)]* .

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of buprenorphine transdermal system increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of buprenorphine transdermal system with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of buprenorphine transdermal system abuse include those with a history of prolonged use of any opioid, including products containing buprenorphine, those with a history of drug or alcohol abuse, or those who use buprenorphine transdermal system in combination with other abused drugs.

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

Buprenorphine transdermal system, like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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

Risks Specific to Abuse of Buprenorphine Transdermal System

Abuse of buprenorphine transdermal system poses a risk of overdose and death. This risk is increased with the concurrent use of buprenorphine transdermal system with alcohol and/or other substances including other opioids and benzodiazepines *[see Warnings and Precautions (5.1, 5.3), Drug Interactions (7)]* .

Buprenorphine transdermal system is approved for transdermal use only.

Intentional compromise of the transdermal delivery system will result in the uncontrolled delivery of buprenorphine and pose a significant risk to the abuser that could result in overdose and death *[see Warnings and Precautions (5.1)].* Abuse may occur by applying the transdermal system in the absence of legitimate purpose, or by chewing, swallowing, snorting, or injecting buprenorphine extracted from the transdermal system.

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

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Do not abruptly discontinue buprenorphine transdermal system in a patient physically dependent on opioids. Rapid tapering of buprenorphine transdermal system in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing buprenorphine transdermal system, gradually taper the dosage using a patient-specific plan that considers the following: the dose of buprenorphine transdermal system the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.1), Warnings and Precautions (5.19)]* .

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)].*

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with buprenorphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]* .

Treatment of Overdose

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

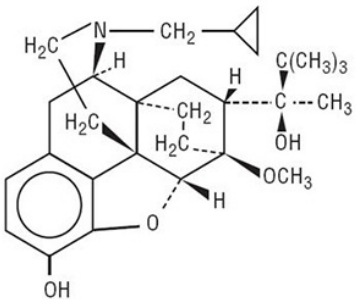
Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. However, naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. High doses of naloxone, 10 mg to 35 mg/70 kg, may be of limited value in the management of buprenorphine overdose. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride (a respiratory stimulant) has also been used.

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

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

11 DESCRIPTION

Buprenorphine is a transdermal system providing systemic delivery of buprenorphine, a mu opioid partial agonist analgesic, continuously for 7 days. The chemical name of buprenorphine is 6,14-ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-α-methyl-, [5α, 7α, (S)]. The structural formula is:



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

System Components and Structure

Five different strengths of buprenorphine transdermal system are available: 5 mcg/hour, 7.5 mcg/hour, 10 mcg/hour, 15 mcg/hour, and 20 mcg/hour (Table 6). The proportion of buprenorphine mixed in the adhesive matrix is the same in each of the five strengths. The amount of buprenorphine released from each system per hour is proportional to the active surface area of the system. The skin is the limiting barrier to diffusion from the system into the bloodstream.

Table 6: Buprenorphine Transdermal System Product Specifications

Buprenorphine Delivery Rate (mcg/hour)	**Active Surface Area (cm^2)**	**Total Buprenorphine Content (mg)**
Buprenorphine transdermal system 5	6.88	5
Buprenorphine transdermal system 7.5	10.313	7.5
Buprenorphine transdermal system 10	13.75	10
Buprenorphine transdermal system 15	20.625	15
Buprenorphine transdermal system 20	27.5	20

Buprenorphine transdermal system is a square, tan-colored system consisting of a protective liner and functional layers. Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a tan-colored web backing layer; (2) a separating layer over the buprenorphine-containing adhesive matrix; (3) the buprenorphine-containing adhesive matrix; and (4) a peel-off release liner. Before use, the release liner covering the adhesive layer is removed and discarded.

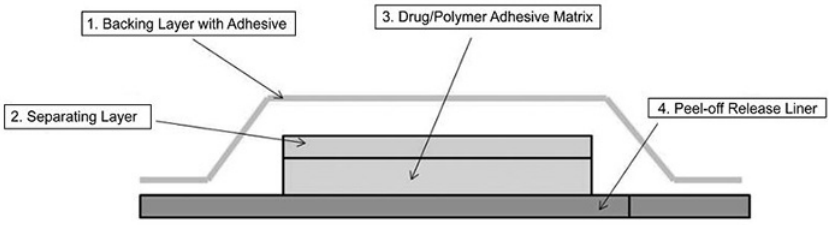


Figure 1: Cross-Section Diagram of Buprenorphine Transdermal System (not to scale).

The active ingredient in buprenorphine transdermal system is buprenorphine. The inactive ingredients in each system are: levulinic acid, citric acid, and acrylate copolymer adhesive.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptors, an agonist at delta-opioid receptors, and a partial agonist at ORL-1 (nociceptin) receptors. The contributions of these actions to its analgesic profile are unclear.

12.2 Pharmacodynamics

Effects on the Central Nervous System

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

Buprenorphine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Buprenorphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

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

Effects on Cardiac Electrophysiology

The effect of buprenorphine transdermal system 10 mcg/hour and 2 x buprenorphine transdermal system 20 mcg/hour on QTc interval was evaluated in a double-blind (buprenorphine transdermal system vs. placebo), randomized, placebo and active-controlled (moxifloxacin 400 mg, open label), parallel-group, dose-escalating, single-dose study in 132 healthy male and female subjects aged 18 to 55 years. The dose escalation sequence for buprenorphine transdermal system during the titration period was: buprenorphine transdermal system 5 mcg/hour for 3 days, then buprenorphine transdermal system 10 mcg/hour for 3 days, then buprenorphine transdermal system 20 mcg/hour for 3 days, then 2 x buprenorphine transdermal system 20 mcg/hour for 4 days. The QTc evaluation was performed during the third day of buprenorphine transdermal system 10 mcg/hour and the fourth day of 2 x buprenorphine transdermal system 20 mcg/hour when the plasma levels of buprenorphine were at steady state for the corresponding doses *[see Warnings and Precautions (5.17)]* .

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

Effects on the Endocrine System

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

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

Effects on the Immune System

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

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with opioid agonists. The minimum effective analgesic concentration of buprenorphine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.4)]*.

Concentration-Adverse Reaction Relationships

There is a relationship between increasing buprenorphine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be

altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.3, 2.4)]* .

12.3 Pharmacokinetics

Absorption

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

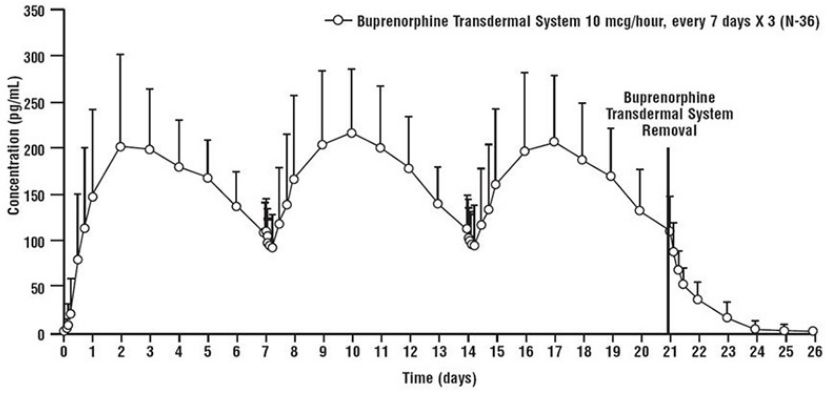


Figure 2

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

Buprenorphine transdermal system 5 mcg/hour, 10 mcg/hour, and 20 mcg/hour provide dose-proportional total buprenorphine exposures (AUC) following 7-day applications. Buprenorphine transdermal system single 7-day application and steady-state pharmacokinetic parameters are summarized in Table 7. Plasma buprenorphine concentrations after titration showed no further change over the 60-day period studied.

Table 7: Pharmacokinetic Parameters of Buprenorphine Transdermal System in Healthy Subjects, Mean (%CV)

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

Transdermal delivery studies showed that intact human skin is permeable to buprenorphine. In clinical pharmacology studies, the median time for buprenorphine transdermal system 10 mcg/hour to deliver quantifiable buprenorphine concentrations (≥25 pg/mL) was approximately 17 hours.

The absolute bioavailability of buprenorphine transdermal system relative to intravenous administration, following a 7-day application, is approximately 15% for all doses (buprenorphine transdermal system
5 mcg/hour, 10 mcg/hour, and 20 mcg/hour).

Effects of Application Site

A study in healthy subjects demonstrated that the pharmacokinetic profile of buprenorphine delivered by buprenorphine transdermal system 10 mcg/hour is similar when applied to the upper outer arm, upper chest, upper back, or the side of the chest *[see Dosage and Administration (2.7)]* .

The reapplication of buprenorphine transdermal system 10 mcg/hour after various rest periods to the same application site in healthy subjects showed that the minimum rest period needed to avoid variability in drug absorption is 3 weeks (21 days) *[see Dosage and Administration (2.7)]* .

Effects of Heat

In a study of healthy subjects, application of a heating pad directly on the buprenorphine transdermal

10 mcg/hour system caused a 26% to 55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed. For this reason, instruct patients not to apply heating pads directly to the buprenorphine transdermal system during system wear *[see Warnings and Precautions (5.6)].*

Fever may increase the permeability of the skin, leading to increased buprenorphine concentrations during buprenorphine transdermal system treatment. As a result, febrile patients are at increased risk for the possibility of buprenorphine transdermal system-related reactions during treatment with buprenorphine transdermal system. Monitor patients with febrile illness for adverse effects and consider dose adjustment *[see Warnings and Precautions (5.7)]* . In a crossover study of healthy subjects receiving endotoxin or placebo challenge during buprenorphine transdermal system 10 mcg/hour wear, the AUC and C_{max}were similar despite a physiologic response of mild fever to endotoxin.

Distribution

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

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

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

Elimination

Metabolism

Buprenorphine metabolism in the skin following buprenorphine transdermal system application is negligible.

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

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

Excretion

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

Following intramuscular administration of 2 mcg/kg dose of buprenorphine, approximately 70% of the dose was excreted in feces within 7 days. Approximately 27% was excreted in urine.

Following transdermal application, buprenorphine is eliminated via hepatic metabolism, with subsequent biliary excretion and renal excretion of soluble metabolites. After removal of buprenorphine transdermal system, mean buprenorphine concentrations decrease approximately 50% within 10 to 24 hours, followed by decline with an apparent terminal half-life of approximately 26 hours. Since metabolism and excretion of buprenorphine occur mainly via hepatic elimination, reductions in hepatic blood flow induced by some general anesthetics (e.g., halothane) and other drugs may result in a decreased rate of hepatic elimination of the drug, leading to increased plasma concentrations.

The total clearance of buprenorphine is approximately 55 L/hour in postoperative patients.

Drug Interaction Studies

Effect of CYP3A4 inhibitors

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

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

administration as well as the specificity of enzyme inhibition *[see Drug Interactions (7)]*.

Effect of CYP3A4 Inducers

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

Specific Populations

Age: Geriatric Patients

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

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

Sex

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

Hepatic Impairment

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

Buprenorphine transdermal system has not been evaluated in patients with severe (Child-Pugh C) hepatic impairment *[see Warnings and Precautions (5.14), Use in Specific Populations (8.6)]* .

Renal Impairment

No studies in patients with renal impairment have been performed with buprenorphine transdermal system.

In an independent study, the effect of impaired renal function on buprenorphine pharmacokinetics after IV bolus and after continuous IV infusion administrations was evaluated. It was found that plasma buprenorphine concentrations were similar in patients with normal renal function and in patients with impaired renal function or renal failure. In a separate investigation of the effect of intermittent hemodialysis on buprenorphine plasma concentrations in chronic pain patients with end-stage renal disease who were treated with a transdermal buprenorphine product (marketed outside the US) up to 70 mcg/hour, no significant differences in buprenorphine plasma concentrations before or after hemodialysis were observed.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

The efficacy of buprenorphine transdermal system has been evaluated in four 12-week double-blind, controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe chronic low back pain or osteoarthritis using pain scores as the primary efficacy variable. Two of these studies, described below, demonstrated efficacy in patients with low back pain. One study in low back pain and one study in osteoarthritis did not show a statistically significant pain reduction for either buprenorphine transdermal system or the respective active comparators.

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

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

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

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

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

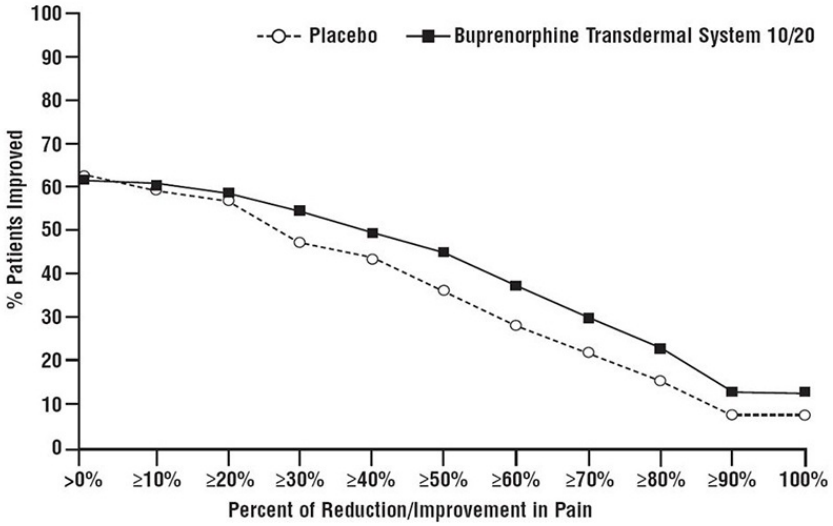


Figure 3: Percent Reduction in Pain Intensity

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

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

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

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

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

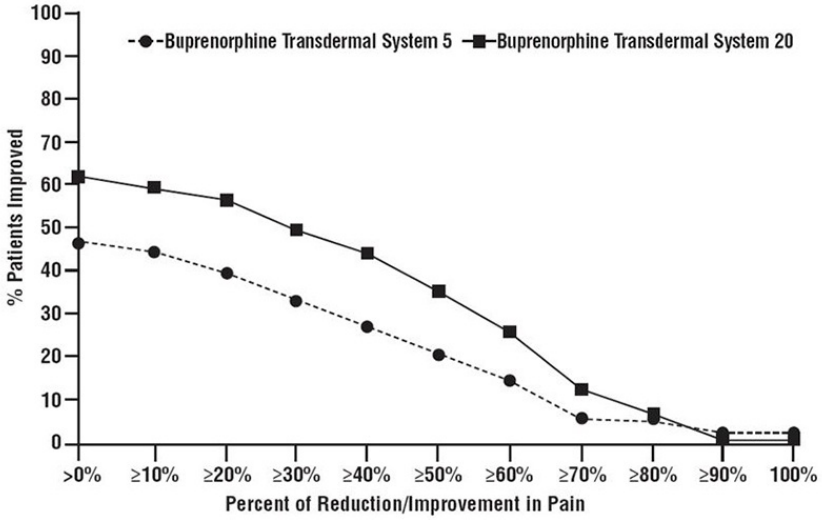


Figure 4: Percent Reduction in Pain Intensity

16 HOW SUPPLIED/STORAGE AND HANDLING

Buprenorphine Transdermal System is supplied in cartons containing 4 individually-packaged systems and a pouch containing 4 Patch-Disposal Units.

Buprenorphine 5 mcg/hour Transdermal Systems are square with rounded corners, tan colored adhesive patches measuring 49 mm by 49 mm. Each system is printed with Buprenorphine Transdermal System CIII 5 mcg/hour with TEVA 3656 and is supplied in a 4-count carton (**NDC 0093-3656-40**).

Buprenorphine 7.5 mcg/hour Transdermal Systems are square with rounded corners, tan colored adhesive patches measuring 54 mm by 54 mm. Each system is printed with Buprenorphine Transdermal System CIII 7.5 mcg/hour with TEVA 3239 and is supplied in a 4-count carton (**NDC 0093-3239-40**).

Buprenorphine 10 mcg/hour Transdermal Systems are square with rounded corners, tan colored adhesive patches measuring 60 mm by 60 mm. Each system is printed with Buprenorphine Transdermal System CIII 10 mcg/hour with TEVA 3657 and is supplied in a 4-count carton (**NDC 0093-3657-40**).

Buprenorphine 15 mcg/hour Transdermal Systems are square with rounded corners, tan colored adhesive patches measuring 66 mm by 66 mm. Each system is printed with Buprenorphine Transdermal System CIII 15 mcg/hour with TEVA 3658 and is supplied in a 4-count carton (**NDC 0093-3658-40**).

Buprenorphine 20 mcg/hour Transdermal Systems are square with rounded corners, tan colored adhesive patches measuring 74 mm by 74 mm. Each system is printed with Buprenorphine Transdermal System CIII 20 mcg/hour with TEVA 3659 and is supplied in a 4-count carton (**NDC 0093-3659-40**).

Store Buprenorphine Transdermal System securely and dispose of properly *[see Patient Counseling Information (17)]* .

Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Storage and Disposal:

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store buprenorphine transdermal system securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving buprenorphine transdermal system unsecured can pose a deadly risk to others in the home *[see Warnings and Precautions (5.1, 5.2), Drug Abuse and Dependence (9.2)]* .

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Buprenorphine transdermal system patches can be disposed of by using the Patch-Disposal Unit *[see Instructions for Use].*Alternatively, expired, unwanted, or unused buprenorphine transdermal system should be disposed of by folding the patch in half and flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse

Inform patients that the use of buprenorphine transdermal system, even when taken as

recommended, can result in addiction, abuse, and misuse, which could lead to overdose and death *[see Warnings and Precautions (5.1)].* Instruct patients not to share buprenorphine transdermal system with others and to take steps to protect buprenorphine transdermal system from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting buprenorphine transdermal system or when the dosage is increased, and that it can occur even at recommended doses.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.2), Overdosage (10)].*

Accidental Exposure

Inform patients that accidental exposure, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]* .

Interaction with Benzodiazepines

Warn patients that it is extremely dangerous to self-administer benzodiazepines while taking buprenorphine transdermal system, and warn patients to use benzodiazepines concurrently with buprenorphine transdermal system only as directed by their physician *[see Drug Interactions (7)]* .

Interaction with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if buprenorphine transdermal system is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.3)]* .

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with buprenorphine transdermal system. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]* .

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered *[see Overdosage (10)]* .

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.9), Adverse Reactions (6.2)].*

Serotonin Syndrome

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

MAOI Interaction

Inform patients to avoid taking buprenorphine transdermal system while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking buprenorphine transdermal system *[see Drug Interactions (7)]* .

Important Administration Instructions

Instruct patients how to properly use buprenorphine transdermal system, including the following:

1. To carefully follow instructions for the application, removal, and disposal of buprenorphine transdermal system. Each week, apply buprenorphine transdermal system to a different site based on the 8 described skin sites, with a minimum of 3 weeks between applications to a previously used site *[see Dosage and Administration (2.7)]* .
2. To apply buprenorphine transdermal system to a hairless or nearly hairless skin site. If none are available, instruct patients to clip the hair at the site and not to shave the area. Instruct patients not to apply to irritated skin. If the application site must be cleaned, use clear water only. Soaps, alcohol, oils, lotions, or abrasive devices should

not be used. Allow the skin to dry before applying buprenorphine transdermal system *[see Dosage and Administration (2.7)]* .
3. To avoid exposing the buprenorphine transdermal system application site to external heat sources, hot water, or prolonged direct sunlight *[see Warnings and Precautions (5.6)].*

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue buprenorphine transdermal system without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.5)].*

Driving or Operating Heavy Machinery

Inform patients that buprenorphine transdermal system may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.20)]* .

Constipation

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

Adrenal Insufficiency

Inform patients that buprenorphine transdermal system could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.11)]* .

Hypotension

Inform patients that buprenorphine transdermal system may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.12)]* .

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in buprenorphine transdermal system. Advise patients how to recognize such a reaction and when to seek medical attention *[see Warnings and Precautions (5.18), Contraindications (4), Adverse Reactions (6)].*

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential the use of buprenorphine transdermal system for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4)], Use in Specific Populations (8.1).*

Embryofetal Toxicity

Inform female patients of reproductive potential that buprenorphine transdermal system can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]* .

Lactation

Advise patients that breastfeeding is not recommended during treatment with buprenorphine transdermal system *[see Use in Specific Populations (8.2)]*

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)].*

Healthcare professionals can contact Teva at 1-888-838-2872 for information on this product.

Manufactured For:
Teva Pharmaceuticals USA, Inc.
Parsippany, NJ 07054

Rev. AB 5/2024

MEDICATION GUIDE

Buprenorphine (bue″ pre nor′ feen) Transdermal System, CIII

Buprenorphine transdermal system is:
- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine, when other pain medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not to be taken on an “as needed” basis.

Important information about buprenorphine transdermal system:

- **Get emergency help or call 911 rightaway if you take too much buprenorphine transdermal system (overdose).** When you first start taking buprenorphine transdermal system, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking buprenorphine transdermal system with other opioid medicines, benzodiazepines, and alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your buprenorphine transdermal system. They could die from taking it. Selling or giving away buprenorphine transdermal system is against the law.
- Store buprenorphine transdermal system securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not use buprenorphine transdermal system if you have:

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

Before applying buprenorphine transdermal system, tell your healthcare provider if you have a history of:

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

Tell your healthcare provider if you are:

- noticing your pain getting worse. If your pain gets worse after you take buprenorphine transdermal system, do not more of buprenorphine transdermal system without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking buprenorphine transdermal system.
- have a fever
- **pregnant or planning to become pregnant.**Use of buprenorphine transdermal system for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.**Not recommended during treatment with buprenorphine transdermal system. It may harm your baby.
- living in a household where there are small children or someone who has abused street or prescription drugs.
- are taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking buprenorphine transdermal system with certain other medicines can cause serious side effects.

When using buprenorphine transdermal system:

- Do not change your dose. Apply buprenorphine transdermal system exactly as prescribed by your healthcare provider. Use the lowest effective dose for the shortest time needed.
- See the detailed Instructions for Use for information about how to apply the buprenorphine transdermal system patch.
- Do not apply a buprenorphine transdermal system patch if the pouch seal is broken, or the patch is cut, damaged, or changed in any way.
- Do not apply more than 1 patch at the same time unless your healthcare provider tells you to.
- You should wear 1 buprenorphine transdermal system patch continuously for 7 days.
- **Call your healthcare provider if the dose you are using does not control your pain.**
- **Do not stop using buprenorphine transdermal system without talking to your healthcare provider.**
- **Dispose of expired, unwanted, or unused buprenorphine transdermal system by using the Patch-Disposal Unit. Alternatively, buprenorphine transdermal system can be disposed of by folding the patch in half and promptly flushing down the toilet, if a drug take-back option is not readily available *[see Instructions for Use]*. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.**

While using buprenorphine transdermal system DO NOT:

- Take hot baths or sunbathe, use hot tubs, saunas, heating pads, electric blankets, heated waterbeds, or tanning lamps. These can cause an overdose that can lead to death.
- Drive or operate heavy machinery, until you know how buprenorphine transdermal system affects you. Buprenorphine transdermal system can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines containing alcohol. Using products containing alcohol during treatment with buprenorphine transdermal system may cause you to overdose and die.

The possible side effects of buprenorphine transdermal system are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, itching, redness or rash where the patch is applied.
  Call your healthcare provider if you have any of these symptoms and they are severe.
  Get emergency medical help or call 911 right away if you have:
- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of buprenorphine transdermal system. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov.**
Manufactured For: **Teva Pharmaceuticals USA, Inc.**, Parsippany, NJ 07054
For more information about buprenorphine transdermal system, call Teva at 1-888-838-2872.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Rev. AB 5/2024

INSTRUCTIONS FOR USE

Buprenorphine Transdermal System (bue″ pre nor′ feen) CIII

Be sure that you read, understand, and follow these Instructions for Use before you usebuprenorphine transdermal system. Talk to your healthcare provider or pharmacist if you have any questions.

Before applyingbuprenorphine transdermal system:

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

Where to applybuprenorphine transdermal system:

- Buprenorphine transdermal system should be applied to the **upper outer arm, upper chest, upper back, or the side of the chest**(**See Figure A**). These 4 sites (located on both sides of the body) provide 8 possible buprenorphine transdermal system application sites.

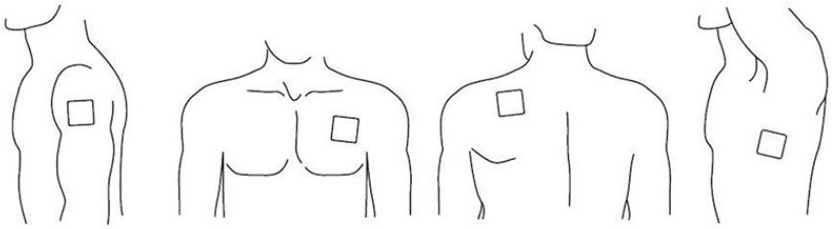


Figure A

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

Figure B

- You should change the skin site where you apply buprenorphine transdermal system each week, making sure that at least 3 weeks (21 days) pass before you re-use the same skin site.
- Apply buprenorphine transdermal system to **a hairless or nearly hairless skin site**. If needed, you can clip the hair at the skin site (**See Figure C**). Do not shave the area. The skin site should not be irritated. **Use only water to clean**the application site. You should not use soaps, alcohol, oils, lotions, or abrasive devices. Allow the skin to dry before you apply the patch.

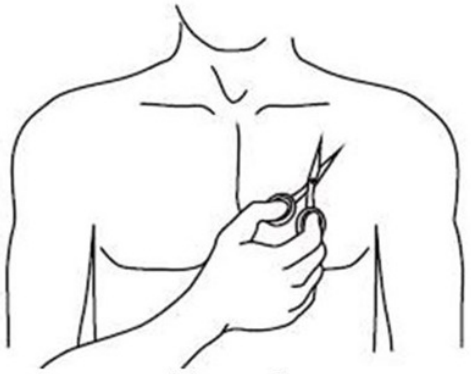


Figure C

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

When to apply a new patch:

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

How to applybuprenorphine transdermal system:

- If you are wearing a patch, remember to remove it before applying a new one.
- Each patch is sealed in its own protective pouch.
- If you are using two patches, remember to apply them at the same site right next to each other. Always apply and remove the two patches together at the same time.
- Use scissors to cut open the pouch along the dotted line (**See Figure D**) and remove the patch. Do not remove the patch from the pouch until you are ready to use it. Do not use patches that have been cut or damaged in any way.

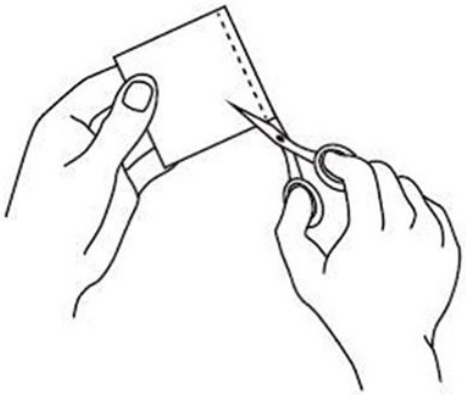


Figure D

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

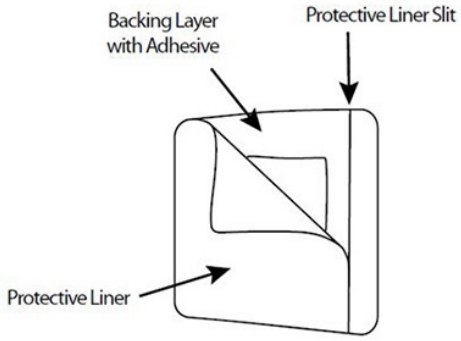


Figure E

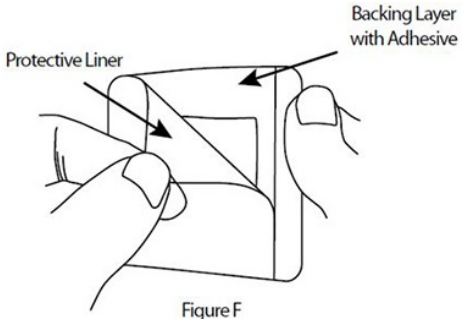


Figure F

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

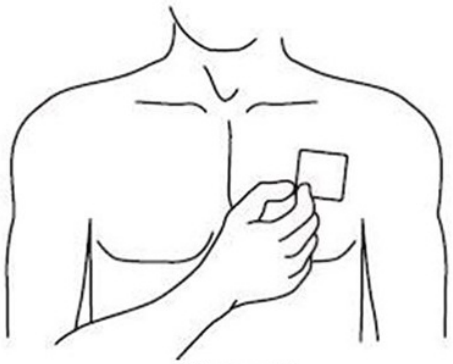


Figure G

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

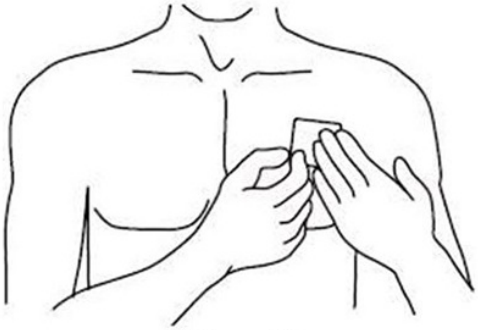


Figure H

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

Figure I

- Make sure that the patch firmly sticks to the skin.
- Go over the edges with your fingers to assure good contact around the patch.
- If you are using two patches, follow the steps in this section to apply them right next to each other.
- Always wash your hands after applying or handling a patch.
- After the patch is applied, write down the date and time that the patch is applied. Use this to remember when the patch should be removed.

If the patch falls off right away after applying, throw it away and put a new one on at a different skin site (**See "Disposing ofbuprenorphine transdermal systempatch")**.

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

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

If the edges of thebuprenorphine transdermal systempatch start to loosen:

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

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

Disposing ofbuprenorphine transdermal systempatch:

Buprenorphine transdermal systempatches should be disposed of by using the Patch-Disposal Unit. Alternatively, the patches can be flushed down the toilet if a drug take-back option is not readily available.

To dispose ofbuprenorphine transdermal systempatches in household trash using the Patch-Disposal Unit:

Remove your patch and follow the directions printed on the Patch-Disposal Unit (**See Figure J**) or see complete instructions below **. Use one Patch-Disposal Unit for each patch.**

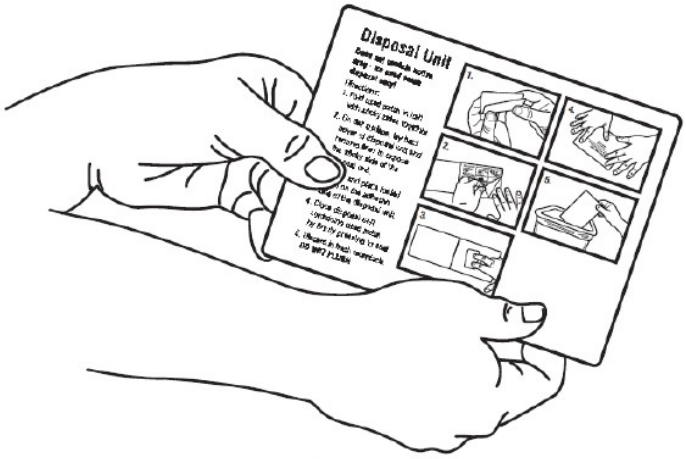


Figure J

1. Fold used patch in half with sticky sides together (**See Figure K**).

Figure K

2. On flat surface, lay back cover of disposal unit and remove liner to expose the sticky side of the disposal unit (**See Figure L**).

Figure L

3. Center and place folded patch on the adhesive side of the disposal unit. (**See Figure M**).

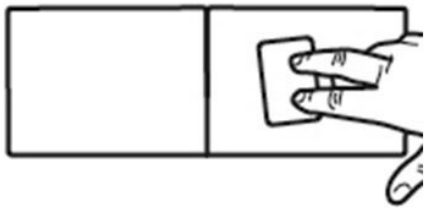


Figure M

4. Close disposal unit containing used patch by firmly pressing to seal (**See Figure N**).

Figure N

5. Discard in trash receptacle (**See Figure O**).

Figure O

Do not put expired, unwanted or unusedpatches in household trash without first sealing them in the Patch-Disposal Unit.

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

To flush yourbuprenorphine transdermal systempatches down the toilet:

Remove your buprenorphine transdermal system patch, fold the sticky sides of a used patch together and flush it down the toilet right away (**See Figure P**).

Figure P

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

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

If you prefer not to flush the used patch down the toilet, and if there is not a drug take-back option readily available, you must use the Patch-Disposal Unit provided to you to discard the patch.

Never put usedbuprenorphine transdermal system patches in the trash without first sealing them in the Patch-Disposal Unit.

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

Brands listed are the trademarks of their respective owners.

Manufactured For:
Teva Pharmaceuticals USA, Inc.
Parsippany, NJ 07054

Rev. AA 7/2023

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 0093-3656-40

Buprenorphine CIII
Transdermal System
5 mcg/hour

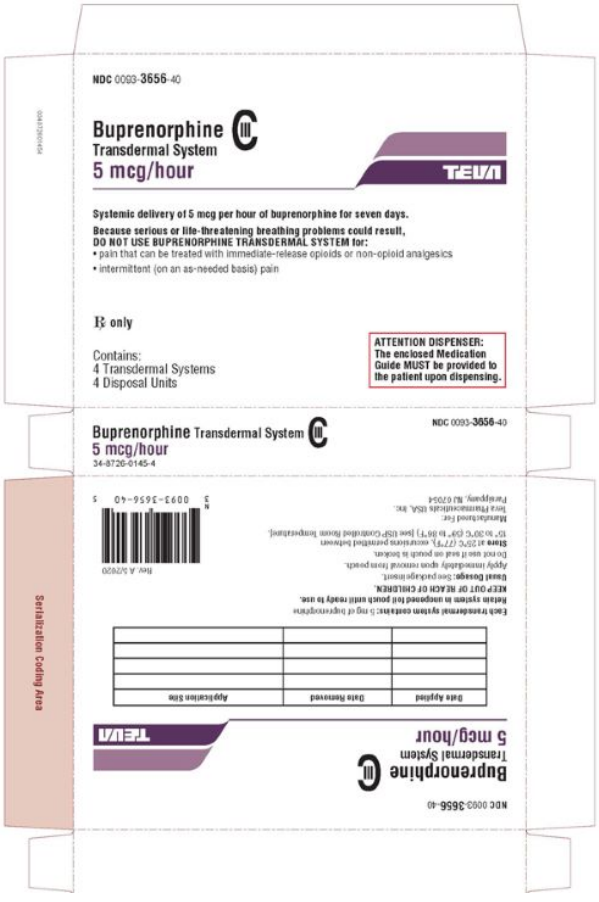
Systemic delivery of 5 mcg per hour of buprenorphine for seven days.

Because serious or life-threatening breathing problems could result,
DO NOT USE BUPRENORPHINE TRANSDERMAL SYSTEM for:
• pain that can be treated with immediate-release opioids or non-opioid analgesics
• intermittent (on an as-needed basis) pain

Rx only

Contains:
4 Transdermal Systems
4 Disposal Units

ATTENTION DISPENSER:
The enclosed Medication Guide MUST be
provided to the patient upon dispensing.



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 0093-3239-40

Buprenorphine CIII
Transdermal System
7.5 mcg/hour

Systemic delivery of 7.5 mcg per hour of buprenorphine for seven days.

Because serious or life-threatening breathing problems could result,
DO NOT USE BUPRENORPHINE TRANSDERMAL SYSTEM for:
• pain that can be treated with immediate-release opioids or non-opioid analgesics
• intermittent (on an as-needed basis) pain

Rx only

Contains:
4 Transdermal Systems
4 Disposal Units

ATTENTION DISPENSER:
The enclosed Medication
Guide MUST be provided to
the patient upon dispensing.

For Use In
Opioid-Experienced
Patients Only

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 0093-3657-40

Buprenorphine CIII
Transdermal System
10 mcg/hour

Systemic delivery of 10 mcg per hour of

buprenorphine for seven days.

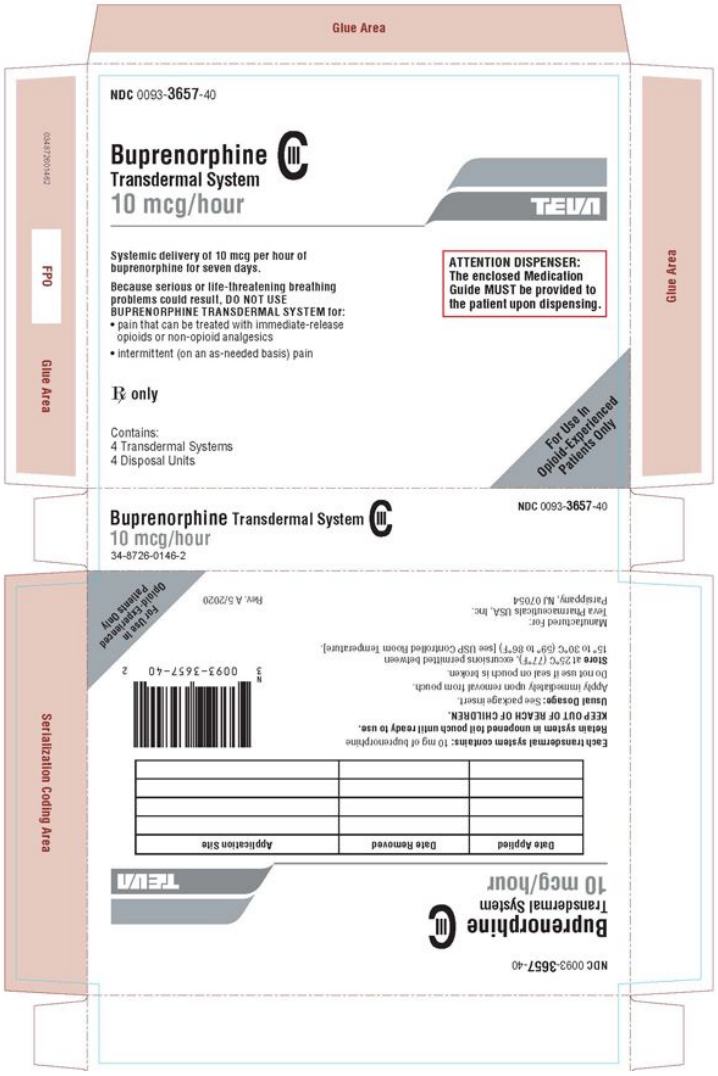
Because serious or life-threatening breathing problems could result, DO NOT USE BUPRENORPHINE TRANSDERMAL SYSTEM for:
• pain that can be treated with immediate-release opioids or non-opioid analgesics
• intermittent (on an as-needed basis) pain

ATTENTION DISPENSER:
The enclosed Medication Guide MUST be provided to the patient upon dispensing.

Rx only

Contains:
4 Transdermal Systems
4 Disposal Units

For Use In
Opioid-Experienced
Patients Only



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 0093-3658-40

Buprenorphine CIII
Transdermal System
15 mcg/hour

Systemic delivery of 15 mcg per hour of buprenorphine for seven days.

Because serious or life-threatening breathing problems could result, DO NOT USE BUPRENORPHINE TRANSDERMAL SYSTEM for:

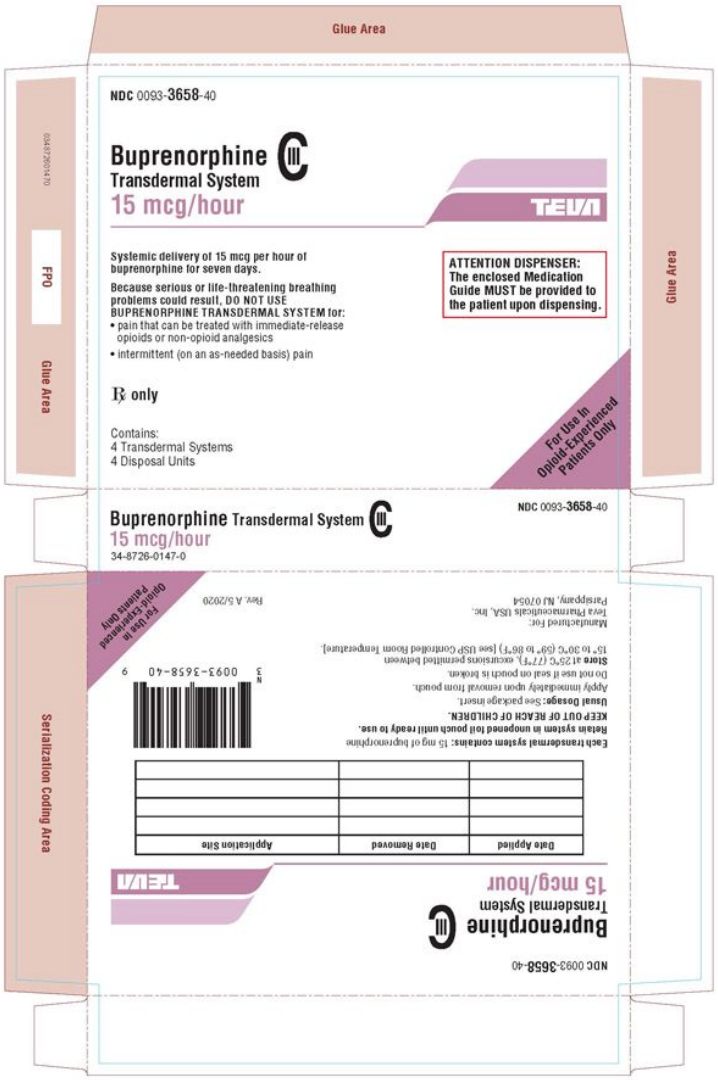
• pain that can be treated with immediate-release opioids or non-opioid analgesics
• intermittent (on an as-needed basis) pain

ATTENTION DISPENSER:
The enclosed Medication Guide MUST be provided to the patient upon dispensing.

Rx only

Contains:
4 Transdermal Systems
4 Disposal Units

For Use In
Opioid-Experienced
Patients Only



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 0093-3659-40

Buprenorphine CIII
Transdermal System
20 mcg/hour

Systemic delivery of 20 mcg per hour of buprenorphine for seven days.

Because serious or life-threatening breathing problems could result, DO NOT USE BUPRENORPHINE TRANSDERMAL SYSTEM for:
• pain that can be treated with immediate-release opioids or non-opioid analgesics
• intermittent (on an as-needed basis) pain

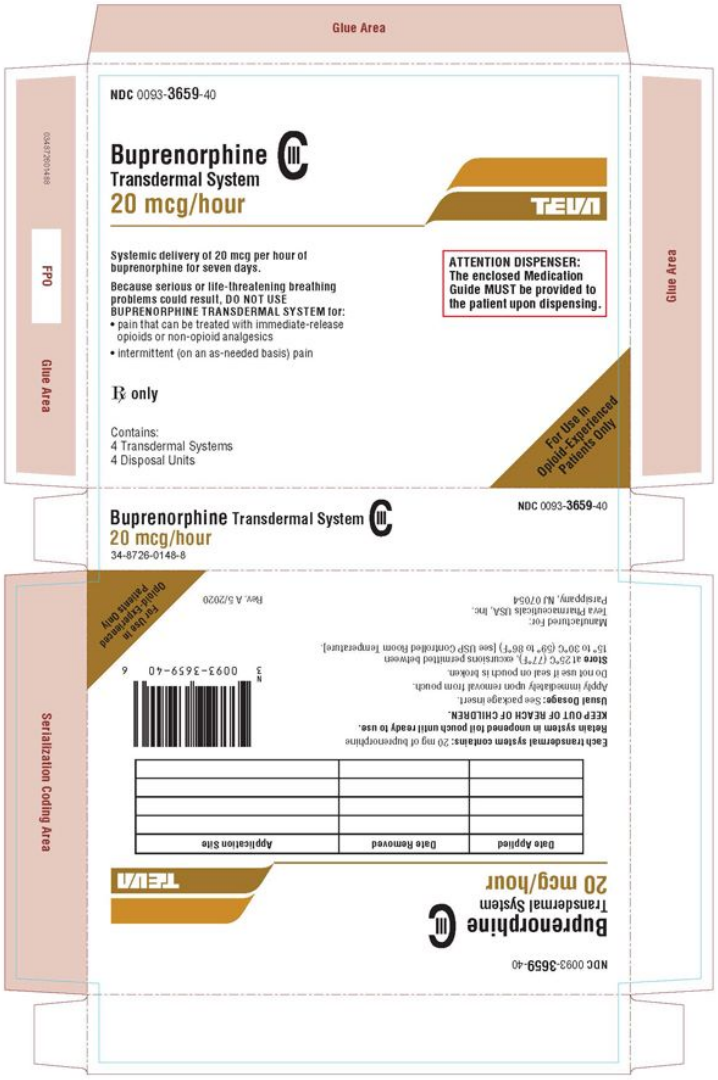
ATTENTION DISPENSER:
The enclosed Medication

Guide MUST be provided to
the patient upon dispensing.

Rx only

Contains:
4 Transdermal Systems
4 Disposal Units

For Use In
Opioid-Experienced
Patients Only



BUPRENORPHINE

buprenorphine patch, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-413
Route of Administration	TRANSDERMAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BUPRENORPHINE (UNII: 40D3SCR4GZ) (BUPRENORPHINE - UNII:40D3SCR4GZ)	BUPRENORPHINE	5 ug in 1 h

Inactive Ingredients	
Ingredient Name	**Strength**
LEVULINIC ACID (UNII: RYX5QG61EI)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	

Packaging			
Item		**Marketing**	**Marketing**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-413-01	4 in 1 CARTON	11/26/2018	
1		1 in 1 POUCH		
1		168 h in 1 PATCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204937	11/26/2018	

BUPRENORPHINE

buprenorphine patch, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-414
Route of Administration	TRANSDERMAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BUPRENORPHINE (UNII: 40D3SCR4GZ) (BUPRENORPHINE - UNII:40D3SCR4GZ)	BUPRENORPHINE	7.5 ug in 1 h

Inactive Ingredients

Ingredient Name	Strength
LEVULINIC ACID (UNII: RYX5QG61EI)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-414-01	4 in 1 CARTON	12/27/2021	
1		1 in 1 POUCH		
1		168 h in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204937	12/27/2021	

BUPRENORPHINE

buprenorphine patch, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-416
Route of Administration	TRANSDERMAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BUPRENORPHINE (UNII: 40D3SCR4GZ) (BUPRENORPHINE - UNII:40D3SCR4GZ)	BUPRENORPHINE	10 ug in 1 h

Inactive Ingredients

Ingredient Name	Strength
LEVULINIC ACID (UNII: RYX5QG61EI)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-416-01	4 in 1 CARTON	11/26/2018	
1		1 in 1 POUCH		
1		168 h in 1 PATCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204937	11/26/2018	

BUPRENORPHINE

buprenorphine patch, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-415
Route of Administration	TRANSDERMAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BUPRENORPHINE (UNII: 40D3SCR4GZ) (BUPRENORPHINE - UNII:40D3SCR4GZ)	BUPRENORPHINE	15 ug in 1 h

Inactive Ingredients	
Ingredient Name	**Strength**
LEVULINIC ACID (UNII: RYX5QG61EI)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-415-01	4 in 1 CARTON	11/26/2018	
1		1 in 1 POUCH		
1		168 h in 1 PATCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204937	11/26/2018	

BUPRENORPHINE

buprenorphine patch, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-417
Route of Administration	TRANSDERMAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BUPRENORPHINE (UNII: 40D3SCR4GZ) (BUPRENORPHINE - UNII:40D3SCR4GZ)	BUPRENORPHINE	20 ug in 1 h

Inactive Ingredients	
Ingredient Name	**Strength**
LEVULINIC ACID (UNII: RYX5QG61EI)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-417-01	4 in 1 CARTON	11/26/2018	
1		1 in 1 POUCH		
1		168 h in 1 PATCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204937	11/26/2018	

Labeler - Praxis, LLC (016329513)

Establishment

Name	Address	ID/FEI	Business Operations

Praxis, LLC		016329513	manufacture(59368-413, 59368-414, 59368-415, 59368-416, 59368-417) , label(59368-413, 59368-414, 59368-415, 59368-416, 59368-417) , pack(59368-413, 59368-414, 59368-415, 59368-416, 59368-417)