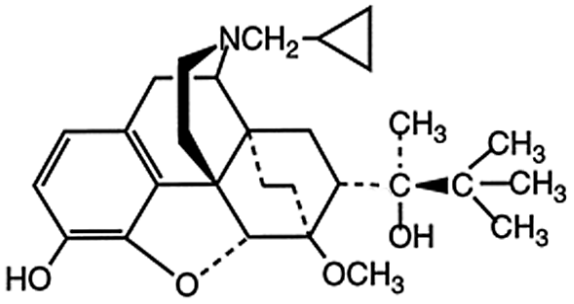
PRODUCT INFORMATION

BUPREDERMAL® TRANSDERMAL DRUG DELIVERY SYSTEM
5, 10, 15, 20, 25, 30 and 40 micrograms per hour

NAME OF THE MEDICINE
Buprenorphine base (active).

The structural formula is:



CAS Registry Number: 52485-79-7

DESCRIPTION
Buprenorphine is 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. The chemical name of buprenorphine is (2S)-2-[17-(cyclopropylmethyl)-4, 5α-epoxy-3-hydroxy-6-methoxy-6α, 14-ethano-14α-morphinan-7α-yl]-3, 3-dimethylbutan-2-ol. The molecular weight is 467.6 and the empirical formula is $C_{29}H_{41}NO_4$.

The inactive ingredients in BUPREDERMAL transdermal drug delivery system (patch) are levulinic acid, oleyl oleate, povidone, Duro Tak 387-2051, Duro Tak 387-2054 and polyethylene terephthalate.

BUPREDERMAL patches are either a rectangular (10, 15, 25, 30 and 40 micrograms per hour), or square (5 and 20 micrograms per hour), beige-coloured, matrix patch with rounded corners, marked with the trade name and consisting of a protective liner and functional layers. Proceeding from the outer surface towards 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 layer ("foil") consisting of polyethylene terephthalate over the adhesive matrix; (4) the buprenorphine-containing adhesive matrix; and (5) a release liner (see Figure 1). Before use the release liner covering the adhesive layer is removed and discarded.

BUPREDERMAL patches are available in seven strengths: 5 micrograms per hour, 10 micrograms per hour, 15 micrograms per hour, 20 micrograms per hour, 25 micrograms per hour, 30 micrograms per hour and 40 micrograms per hour. The composition of all seven strengths is identical except for patch size. The proportion of buprenorphine in the adhesive

matrix is the same in each strength (10% by weight). The amount of buprenorphine released from each system per hour is proportional to the surface area of the patch. The skin is the limiting barrier to diffusion from the system into the bloodstream.

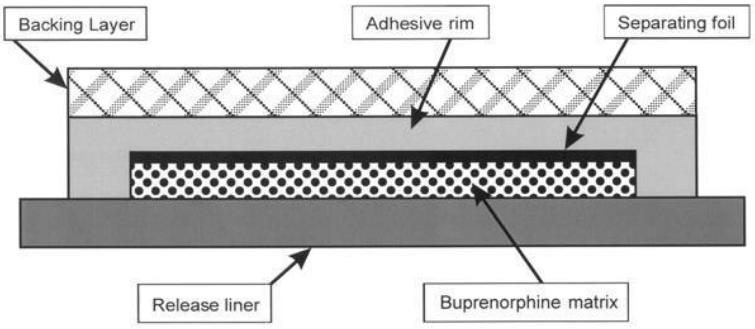


Figure 1 Cross section drawing of BUPREDERMAL patch

PHARMACOLOGY

Pharmacodynamics

Buprenorphine is a partial opioid agonist, acting at mu-opioid receptors. The opioid agonist activities are dose related. Buprenorphine also has antagonistic activity at the kappa-opioid receptor. It is classified as a psychotropic substance under international convention.

Like other opioid agonists, buprenorphine produces dose-related analgesia, however a ceiling effect to analgesia is well documented. Buprenorphine binds to and dissociates from the mu-receptor slowly, which may account for the prolonged duration of analgesia and, in part, for the limited physical dependence potential observed with the drug.

Buprenorphine produces similar effects to other opioids on the central nervous, cardio-vascular, respiratory and gastrointestinal systems, although the intensity and duration of the effects may vary when compared with other opioids. Opioids may also influence the hypothalamic-pituitary-adrenal or –gonadal axes, including an increase in serum prolactin and decreases in plasma cortisol and testosterone, which can manifest in clinical symptoms.

Since kappa-receptor agonist activity is related to psychotomimetic and dysphoric effects, buprenorphine is expected to produce fewer psychotomimetic and dysphoric effects than drugs with kappa-agonist activities.

Like other opioid agonists, buprenorphine may produce increases in cerebrospinal fluid pressure, cause altered mentation, mental clouding or amnesia.

Buprenorphine acts to reduce blood pressure in a manner similar to other opioids. BUPREDERMAL patch application resulted in transient decreases in blood pressure in healthy young and elderly subjects, without clinical adverse events.

Like other opioid analgesics, buprenorphine has a potential of respiratory depression. Respiratory depression is less common than with full mu-agonists, such as morphine and there appears to be a ceiling effect. However, evidence suggests that buprenorphine is a partial agonist with respect to its respiratory depressant activity. When respiratory depression occurs it appears to have a slower onset and longer duration compared with morphine.

Administration of buprenorphine to persons who are physically dependent on full mu-opioid

agonists may precipitate an abstinence syndrome depending on the level of physical dependence, and the timing and dose of buprenorphine.

Like other opioids buprenorphine may cause nausea, vomiting, constipation and an increase in biliary tract pressure. Effects on the immune system were seen with natural opioids like morphine in *in vitro* and animal studies, although the clinical significance of these is unknown. It is not known whether buprenorphine, a semi-synthetic opioid, has immunological effects similar to morphine.

Buprenorphine can cause dose-related miosis and urinary retention in some patients.

Pharmacokinetics

Each BUPREDERMAL patch provides a steady delivery of buprenorphine for up to seven days. Steady state is achieved by day three following the first application. After removal of a BUPREDERMAL patch, buprenorphine concentrations decline, decreasing approximately 50% in 12 hours (range 10 to 24 hours).

BUPREDERMAL patches 5 micrograms per hour, 10 micrograms per hour, 15 micrograms per hour, 20 micrograms per hour, 25 micrograms per hour, 30 micrograms per hour and 40 micrograms per hour provide dose-proportional increases in total exposure (AUC) over the seven-day application period. Dose-proportional increases in plasma concentrations occur at steady state with BUPREDERMAL patch application for up to 60 days. Accumulation of plasma buprenorphine did not occur during the 60 days.

The rate of buprenorphine release from each patch is proportional to the surface area. Each BUPREDERMAL patch 5 micrograms releases 5 micrograms of buprenorphine per hour, and contains a total of 5 mg of buprenorphine. Each BUPREDERMAL patch 10 micrograms releases 10 micrograms of buprenorphine per hour and contains a total of 10 mg of buprenorphine. Each BUPREDERMAL patch 15 micrograms releases 15 micrograms of buprenorphine per hour and contains a total of 15 mg of buprenorphine. Each BUPREDERMAL patch 20 micrograms releases 20 micrograms of buprenorphine per hour and contains a total of 20 mg of buprenorphine. Each BUPREDERMAL patch 25 micrograms releases 25 micrograms of buprenorphine per hour and contains a total of 25 mg of buprenorphine. Each BUPREDERMAL patch 30 micrograms releases 30 micrograms of buprenorphine per hour and contains a total of 30 mg of buprenorphine. Each BUPREDERMAL patch 40 micrograms releases 40 micrograms of buprenorphine per hour and contains a total of 40 mg of buprenorphine.

Absorption

Following BUPREDERMAL patch application, buprenorphine diffuses from the patch through the skin. In clinical pharmacology studies, the median time for BUPREDERMAL patch 10 micrograms to deliver detectable buprenorphine concentrations (25 picograms/mL) was approximately 17 hours. The mean bioavailability of buprenorphine from a BUPREDERMAL patch relative to intravenous (IV) dosing is between 13-15% (for all strengths).

Accidental oral ingestion

Measurable systemic levels of buprenorphine were demonstrated in dogs given BUPREDERMAL patches by oral administration.

Distribution

Buprenorphine is approximately 96% bound to plasma proteins.

In a study of IV buprenorphine in healthy subjects, the volume of distribution at steady state was 430 L, which is indicative of the high 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 concentrations appear to be approximately 15% to 25% of concurrent plasma concentrations.

Metabolism and elimination
Buprenorphine metabolism in the skin following BUPREDERMAL patch application is negligible. 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; norbuprenorphine is also glucuronidated prior to elimination. Buprenorphine is eliminated in the faeces within seven days.

Norbuprenorphine is the only known active metabolite of buprenorphine. It has been shown to be a respiratory depressant in rats at concentrations at least 50-fold those seen following application of BUPREDERMAL patch 20 micrograms per hour.

In a study in postoperative patients the total clearance of buprenorphine was 55 L/h.

Application site
A study in healthy subjects demonstrated that the pharmacokinetic profile of buprenorphine delivered by BUPREDERMAL patch 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 applying BUPREDERMAL patches repeatedly to the same site, immediate reapplication caused increased absorption, without clinical adverse events. For this reason, rotation of application sites is recommended (see DOSAGE AND ADMINISTRATION).

In another study in healthy subjects, application of a heating pad directly on the BUPREDERMAL patch caused a transient, 26 to 55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within five hours after the heat was removed. For this reason, applying heat sources such as hot water bottles, heat pads or electric blankets directly to the BUPREDERMAL patch is not recommended. A heating pad applied to a BUPREDERMAL patch site directly after patch removal did not alter absorption from the skin depot.

CLINICAL TRIALS

The safety and efficacy of BUPREDERMAL patches in the management of chronic pain has been studied in 30 clinical trials [4867 patients treated with BUPREDERMAL patches]. The active and placebo-controlled clinical trials included patients with moderate to severe chronic pain of osteoarthritis, low back and non-cancer pain requiring opioid analgesia. A single trial examined the safety of three doses of BUPREDERMAL patches given for 72 hours to patients following orthopaedic surgery. No trials have been conducted in patients with cancer-related pain.

BUPN.CLIN0001 was a randomised, double-blind, double-dummy, parallel, equivalence study comparing the efficacy and tolerability of BUPREDERMAL patches 5, 10 and 20 mg

applied every seven days with sublingual buprenorphine tablets 200 and 400 micrograms [Temgesic] in 238 patients with moderate to severe pain due to osteoarthritis [hip and/or knee, 85% > one year]. Patients were titrated to optimum pain control over 21 days, and continued at this level for 28 days. Paracetamol was permitted for breakthrough pain and all usage recorded. The primary efficacy variable was pain intensity recorded during the assessment period [Days three and seven, BS-11 scale, refer Table 1]. The Per Protocol (PP) population mean reductions in pain scores ranged from 2.6 to 3.6 across the three daily rating assessments [morning, midday, evening] and the estimated mean difference between both active treatment arms was minimal [range 0.001 to 0.13]. The 95% confidence intervals for the difference between treatments were within the range -1 to 1, compared with the pre-specified equivalence margins of -1.5 to 1.5. This demonstrated equivalent efficacy. At study completion
70% [40/51] of patients on the patch and 75% [42/51] on tablets rated their pain relief as good or very good.

Table 1 Pain intensity scores in study BUPN.CLIN0001

	Transdermal buprenorphine patches	**Sublingual buprenorphine tablets**
Dose	Titration to optimum pain control over 21 days with same dose continued for up to 28 days	200 or 400 micrograms 6 – to 8-hourly
Mean baseline pain intensity*	6.1	6.3
Mean pain intensity scores during assessment [Day 7]*	3.2	3.2

There was no difference in escape medication usage and the incidence of discontinuation due to lack of efficacy was similar between the two treatment groups [9% Temgesic vs 14% BUPREDERMAL patch]. The most common adverse events reported were those commonly associated with the use of opioids [nausea, vomiting, dizziness, somnolence, headache and constipation].

BP98-1201 was a randomised, double-blind trial comparing the efficacy and safety of BUPREDERMAL patches 5, 10 and 20 mg, applied every seven days, with hydrocodone/paracetamol [2.5 mg/250 mg] tablets four times a day (qid) in 270 patients with chronic moderate to severe back pain [pain intensity $\geq$ 5 BS-11 scale], not controlled by non-opioid analgesia alone [ibuprofen 400 mg qid]. Patients were titrated to optimum pain control over 21 days, and continued at this level for 35 days. The primary efficacy variables were average pain intensity [BS-11 scale*] and patient satisfaction with medication over Days 21-56†, refer Table 2. The Intention to Treat (ITT) population mean baseline pain intensity was 7.74 [BUPREDERMAL patch group] compared with 7.65, which reduced through Days 21-56 to 5.96 and 6.04, respectively. The difference [and 95% confidence interval] in average pain intensity between the two treatments was -0.08 [-0.06 to 0.44]. The difference between the two treatments in patient global satisfaction was 0.16 [-0.08 to 0.39]. BUPREDERMAL patches were equally effective as hydrocodone/paracetamol tablets in relieving pain and for patient satisfaction.

Table 2 Pain intensity scores in study BP98-1201

	Transdermal buprenorphine patches	**Hydrocodone/paracetamol tablets**
Dose	Titration to optimum pain control over 21 days, with same dose continued for 35 days	1 to 3 hydrocodone/paracetamol [2.5mg/250mg] tablets four times daily

Mean baseline pain intensity*	7.74 [7.5 to 8.0]	7.65 [7.4 to 7.9]
Reduction in pain intensity from baseline to end of study*	1.78	1.61
Average pain intensity over Days 21-56*	5.96 [5.6 to 6.3]	6.04 [5.7 to 6.4]
Patient global satisfaction with medication over Days 21-56†	1.53 [1.4 to 1.7]	1.37 [1.2 to 1.5]

The majority of adverse events reported were mild or moderate in severity and were typically associated with opioid therapy. Withdrawals due to lack of efficacy was similar for both groups (15% for BUPREDERMAL patch and 14% for hydrocodone/paracetamol). No changes in laboratory values were considered related to treatment, and no clinically important changes were reported for pulse rate, respiratory rate or physical examinations.

* Pain intensity was assessed by the BS-11 pain scale, an 11-point scale for rating current pain, where 0 = "no pain" and 10 = "pain as bad as you can imagine".

† Patient global satisfaction with medication was assessed on a 4-point scale, with the question "Rate the study medication you received for pain".

INDICATIONS

Management of moderate to severe pain.

CONTRAINDICATIONS

BUPREDERMAL patches are contraindicated in patients with known hypersensitivity to buprenorphine or any components of the patch, *myasthenia gravis*, *delirium tremens* and pregnancy.

BUPREDERMAL patches are contraindicated in patients with severely impaired respiratory function and in patients concurrently receiving non-selective monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with non-selective MAOIs.

BUPREDERMAL patches must not be used for the treatment of opioid dependence and opioid withdrawal.

PRECAUTIONS

General

In chronic non-malignant pain, medication modifies the pain only to some extent. A comprehensive assessment is essential, and non-pharmacological options should be explored before starting pharmacological therapy. Patients should be advised about the expected outcome of therapy (i.e. pain reduction rather than complete abolition of pain, reduced suffering, improved function and quality of life). Opioid therapy should be initiated as a trial. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment with an opioid analgesic. Reassess or discontinue opioid therapy if there is no improvement of pain and/or function. BUPREDERMAL should be ceased if there is any evidence of misuse or abuse, or if BUPREDERMAL is having a detrimental effect.

BUPREDERMAL is not suitable as an as-needed (prn) analgesic due to its delayed onset of action.

BUPREDERMAL patches should be used with particular caution in patients with convulsive disorders, head injury, shock, a reduced level of consciousness of uncertain origin, intracranial lesions or increased intracranial pressure and severe hepatic impairment. Buprenorphine may lower the seizure threshold in patients with a history of seizure disorder. Use with caution in patients with hypotension, hypovolaemia, biliary tract disease, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, chronic renal and hepatic disease and debilitated patients. As with all opioids, a reduction in dosage may be advisable in hypothyroidism.

Use in surgery

BUPREDERMAL patches are not recommended for analgesia in the immediate post-operative period or in other situations characterised by a narrow therapeutic index or a rapidly varying analgesic requirement. As with all opioid preparations, patients who are to undergo cordotomy or other pain-relieving surgical procedures should not use BUPREDERMAL patches for at least 24 hours prior to surgery. BUPREDERMAL patches should be used with caution following abdominal surgery, as opioids are known to impair intestinal motility.

Respiratory depression

Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when addicts have intravenously abused buprenorphine, usually with benzodiazepines concomitantly. Additionally, overdosage deaths due to ethanol and benzodiazepines in combination with buprenorphine have been reported. Caution should be exercised when prescribing BUPREDERMAL patches to patients known to have, or suspected of having, problems with drug or alcohol abuse or serious mental illness.

Prolongation of QT interval

In a positive-controlled study of the effect of BUPREDERMAL patches on the QTc interval in healthy subjects, therapeutic dosages (10 micrograms per hour) had no effect on the QTc interval but higher dosages (40 micrograms per hour) were associated with a mean prolongation of the QTc interval of 5.9 ms. Consider these observations in clinical decisions when prescribing BUPREDERMAL to patients with electrolyte abnormalities and cardiac conditions that may elevate the risk of QT prolongation, patients with congenital QT prolongation, or those taking Class IA antiarrhythmic medications (e.g., quinidine, disopyramide), Class III antiarrhythmic medications (e.g., sotalol, amiodarone) or any other medication which prolongs the QT interval.

Gastrointestinal tract

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of buprenorphine. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution is advised in patients with chronic constipation. If paralytic ileus is present or suspected, treatment with BUPREDERMAL should be stopped.

Febrile illness

A kinetic study indicated 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, severe febrile illness may increase the rate of buprenorphine absorption from the patch and thus, patients with severe febrile illness should be monitored for side effects and may require dose adjustment.

Psychological dependence (addiction), abuse, misuse and diversion

Controlled human and animal studies indicate that buprenorphine has a lower dependence liability than pure agonist analgesics. In humans, limited euphorigenic effects have been observed with buprenorphine.

However, as with other opioids, there is a potential for abuse of the drug and for development of strong psychological dependence.

Although the risk of addiction in any individual is unknown, it may occur in patients appropriately prescribed BUPREDERMAL and in those who obtain the drug illicitly. Psychological and/or physical dependence may occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for addiction to opioids, abuse, or misuse prior to prescribing BUPREDERMAL and monitor all patients receiving BUPREDERMAL for the development of these behaviours or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression).

The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids, but use in such patients necessitates comprehensive counselling about the risks and proper use of opioids, along with close monitoring for signs of addiction, abuse, or misuse.

BUPREDERMAL, like other opioids, can be diverted for non-medical use into illicit channels of distribution. BUPREDERMAL should therefore be prescribed and handled with a high degree of caution appropriate to the use of a drug with strong abuse potential.

BUPREDERMAL is intended for transdermal use only. Abuse of opioids poses a risk of overdose and death. This risk is increased with concurrent abuse of opioids with alcohol and other substances including other opioids and benzodiazepines. Abuse or misuse in ways other than indicated or intentional compromise of transdermal delivery systems containing opioids will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see OVERDOSAGE).

Physical Dependence and tolerance

Both tolerance and physical dependence can develop during chronic opioid therapy. Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Withdrawal symptoms may occur following abrupt discontinuation of opioids. Therefore, BUPREDERMAL should not be abruptly discontinued (see DOSAGE AND ADMINISTRATION). If BUPREDERMAL is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Withdrawal may also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, or mixed agonist/antagonist analgesics (pentazocine).

Opioid-naïve patients

The lowest dose available, BUPREDERMAL patch 5 micrograms, should be used as the starting dose in opioid-naïve patients.

Renal impairment

No dose adjustment is necessary in patients with renal impairment.

Hepatic impairment

Buprenorphine is metabolised in the liver. No dose adjustment is necessary in patients with mild to moderate hepatic impairment, however, the intensity and duration of its action may be affected in patients with impaired liver function. Patients with severe hepatic impairment may accumulate buprenorphine during BUPREDERMAL patch treatment. Consideration should be given to alternative therapy and BUPREDERMAL patches should be used with caution, if at all, in such patients.

Application of External Heat

Advise patients and their caregivers to avoid exposing the application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds while wearing the patch because an increase in absorption of buprenorphine may occur. There is a potential for temperature-dependent increases in buprenorphine released from the patch, thereby increasing the risk of opioid reactions.

Driving and operating dangerous machinery

BUPREDERMAL patch has a major influence on the ability to drive and use machines. Even when used according to instructions, buprenorphine may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility such that road safety and the ability to operate machinery may be impaired. This applies particularly in the beginning of treatment, during titration to a higher dose and in conjunction with other centrally acting substances including alcohol, tranquilisers, sedatives and hypnotics. If affected, patients should not drive or operate machinery nor for at least 24 hours after the patch has been removed.

Effects on fertility

No adverse effects on fertility or embryonic development were seen in rats when treated males were paired with treated females (≤20 mg patch every 3 days). Exposure (AUC) with these doses are up to 70 times greater than the expected daily systemic exposure (AUC) of buprenorphine in humans during treatment with BUPREDERMAL 40 mg patch.

Use in pregnancy

Buprenorphine has been shown to cross the placenta in humans and has been detected in newborn blood, urine and meconium. Opioid analgesics, including buprenorphine, may cause respiratory depression in the newborn infant. Withdrawal symptoms in newborn infants have been reported with prolonged use of this class of drugs. Neonatal withdrawal symptoms may include poor feeding, diarrhoea, irritability, tremor, rigidity, and seizures. Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms. There are no adequate and well-controlled studies of buprenorphine or BUPREDERMAL patches in pregnant women

No effects on embryofetal development were noted in studies with topically applied BUPREDERMAL patches to pregnant rats (≤20 mg patch) and rabbits (80 mg patch), and in studies in rabbits that received daily SC injections of buprenorphine during the period of organogenesis (≤5 mg/kg/day). Exposures (AUC) at these doses were 47 and 74 times in rats and rabbits, respectively, the expected daily systemic exposure (AUC) of buprenorphine in humans during treatment with BUPREDERMAL 40 mg patch.

In a pre/postnatal study in pregnant and lactating rats, administration of ≥0.5 mg/kg/day SC buprenorphine caused an increase in the number of stillbirths and reduced pup survival. Exposures (AUC) at the no effect level (0.05 mg/kg/day SC) were subclinical.

Use in lactation
Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. Decreases in postnatal survival, growth and development were also observed in animals treated with buprenorphine during lactation. Buprenorphine passes into mother's milk at low concentrations and therefore BUPREDERMAL patches should not be used by breastfeeding women.

Paediatric use
The safety and efficacy of BUPREDERMAL patches in patients under 18 years of age has not been established. BUPREDERMAL is not recommended for use in children.

Genotoxicity
Buprenorphine showed no evidence of genotoxic activity in assays for gene mutations (reverse mutations in bacterial cells, forward mutations in mammalian cells and yeast), chromosomal damage (human lymphocytes, mouse micronucleus test, Chinese hamster cell *in vivo* and *in vitro*) or gene conversion (yeast). However, in other assays, buprenorphine was positive for frame-shift mutations in Ames test and caused inhibition of normal DNA synthesis and increases in unscheduled DNA synthesis in studies using mouse testes.

Carcinogenicity
No evidence of carcinogenicity was seen in Tg.AC transgenic mice treated with dermal doses of buprenorphine up to 600 mg/kg/day for 6 months or female rats treated with daily dermal doses of buprenorphine up to 200 mg/kg/day for approximately 100 weeks. These doses resulted in exposures (AUC) at least 160 times the expected daily systemic dose of buprenorphine in humans during treatment with BUPREDERMAL 40 mg patch. In male rats, however, an increased incidence of benign testicular interstitial tumours was observed in animals treated dermally with ≥60 mg/kg/day buprenorphine for approximately 100 weeks. Exposure (AUC) at the NOEL was 96 times greater than the expected daily systemic exposure of buprenorphine in humans during treatment with BUPREDERMAL 40 mg patch.

Effect on laboratory tests
Increased alanine aminotransferase levels.

INTERACTIONS WITH OTHER MEDICINES

Anti-arrhythmic medications
Higher doses (40 micrograms per hour) of buprenorphine may increase the QTc interval. This should be considered when prescribing BUPREDERMAL patches for patients with congenital QT prolongation or those taking anti-arrhythmic medications in either class IA (e.g. quinidine, procainamide) or in Class III (e.g. amiodarone, sotalol) or any other medication which prolongs the QT interval.

Anti-ulcer medication
In clinical trial patients there were no apparent effects on BUPREDERMAL patch exposure when used concomitantly with various H_2-antagonists or proton pump inhibitors.

CNS depressants

BUPREDERMAL patches, like all opioid analgesics, should be used with caution in patients who are currently taking other CNS depressants or other drugs that may produce additive depressant effects, e.g. respiratory depression, hypotension, profound sedation or potentially result in coma or death. Such agents include opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages.

CYP inhibitors and inducers

Buprenorphine is both a substrate for, and an inhibitor of, CYP3A4. Specific inhibitors of CYP3A4 (ketoconazole, ritonavir, indinavir) have been shown to inhibit formation of the buprenorphine metabolite, norbuprenorphine, in human liver microsomes. Antifungal drugs with similar CY3A4 inhibiting properties to ketoconazole include fluconazole and itraconazole).

One drug interaction study with ketoconazole did not produce clinically relevant increases in mean maximum or total buprenorphine exposure; however, caution is advised when BUPREDERMAL patches are administered concurrently with inhibitors of CYP3A4 (e.g. protease inhibitors, some drug classes of azole antimycotics, calcium channel antagonists and macrolide antibiotics) as this might lead to increased levels with increased efficacy of buprenorphine with concomitant increased toxicity.

Unlike BUPREDERMAL patches, oral dose buprenorphine-containing formulations refer to an interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) that resulted in increased C_{max} and AUC of buprenorphine (approximately 50% and 70% respectively) and, to a lesser extent, of norbuprenorphine. Patients should be closely monitored, and may require a dose reduction if combining oral dose buprenorphine-containing formulations with CYP3A4 inhibitors.

The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied; however, co- administration of BUPREDERMAL patches and enzyme inducers (e.g. phenobarbitone, carbamazepine, phenytoin, rifampicin) could lead to increased clearance which might result in reduced efficacy. Buprenorphine has also been shown to be a CYP2D6 inhibitor *in vitro*.

General anaesthetics

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 buprenorphine.

Monoamine oxidase inhibitors

Non-selective MAOIs intensify the effects of opioid drugs which can cause anxiety, confusion and respiratory depression. BUPREDERMAL patches must not be used concomitantly with non- selective MAOIs or in patients who have received non-selective MAOIs within the previous 14 days. As it is unknown whether there is an interaction between selective MAOIs (e.g. selegiline) and buprenorphine, caution is advised with this drug combination.

Warfarin

The potential exists for international normalized ratio (INR) elevation in patients who are concomitantly taking warfarin. A retrospective safety analysis and benefit-risk assessment was performed evaluating the interaction between buprenorphine and warfarin. The analysis revealed very limited data was available and that there was a more likely interaction between buprenorphine and phenprocoumon than warfarin. However, there is not sufficient information for inclusion of the medicine interaction between buprenorphine and phenprocoumon.

Anticholinergics

Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when BUPREDERMAL is used concurrently with anticholinergic drugs.

ADVERSE EFFECTS

Adverse reactions that may be associated with BUPREDERMAL patch therapy in clinical use are similar to those observed with other opioid analgesics and tend to reduce with time, with the exception of constipation.

The following adverse reactions have been reported.

Cardiac disorders

Uncommon	angina pectoris, palpitations, tachycardia

Ear and labyrinth disorders

Uncommon	tinnitus, vertigo
Very rare	ear pain

Eye disorders

Uncommon	dry eye, vision blurred
Rare	eyelid oedema, miosis, visual disturbance

Gastrointestinal disorders

Very Common	constipation*, dry mouth, nausea*, vomiting*
Common	abdominal pain*, diarrhoea*, dyspepsia*
Uncommon	flatulence
Rare	diverticulitis*, dysphagia, ileus, pyrosis (heartburn)
Very rare	retching

General disorders and administration site conditions

Very common	application site reaction (includes erythema, oedema, pruritus or rash at the application site)
Common	asthenic conditions* (including muscle weakness, lethargy, fatigue and malaise), chest pain*, pain, peripheral oedema, tiredness
Uncommon	application site dermatitis (late onset local allergic reactions with marked signs of inflammation - in such cases, discontinue BUPREDERMAL patch), influenza-like illness, oedema, pyrexia*, rigors*, withdrawal syndrome

Hepatobiliary disorders

Rare	biliary colic

Immune system disorders

Uncommon	allergic reaction (including oropharyngeal swelling and swollen tongue)
Rare	anaphylactic responses
Very rare	serious allergic reactions

Injury, poisoning and procedural complications

Uncommon	accidental injury (including fall)

Metabolism and nutrition disorders

Common	anorexia
Uncommon	dehydration*, weight decreased

Musculoskeletal and connective tissue disorders

Uncommon	muscle cramps, muscle spasm, myalgia
Very rare	muscle fasciculation

Nervous system disorders

Very Common	dizziness, headache*, somnolence*
Common	dysgeusia (taste disturbance), paraesthesia, tremor
Uncommon	concentration impairment, coordination abnormal, dysarthria, hypoaesthesia, memory impairment, migraine, restlessness, sedation, sleep disorder, syncope*
Rare	dysequilibrium, numbness
Unknown	convulsions

Psychiatric disorders

Common	anxiety, confusion, depression*, insomnia, nervousness
Uncommon	affect lability, agitation, aggression, depersonalisation, euphoric mood, hallucination, libido decreased, nightmare
Rare	psychotic disorder
Very rare	dependence, mood swings

Renal and urinary disorders

Uncommon	urinary incontinence, urinary retention
Rare	urinary hesitation

Reproductive system and breast disorders

Rare	decreased erection, sexual dysfunction

Respiratory, thoracic and mediastinal disorders

Common	dyspnoea*
Uncommon	asthma aggravated*, cough, hiccups, hyperventilation, hypoxia, rhinitis*, wheezing*
Rare	respiratory depression, respiratory failure*

Skin and subcutaneous tissue disorders

Very Common	pruritus*
Common	exanthema, rash*, sweating*
Uncommon	dermatitis contact (in some cases, late onset reactions occurred with marked signs of inflammation - in such cases, discontinue BUPREDERMAL patch), dry skin, face oedema, urticaria
Very rare	pustules, vesicles

Vascular disorders

Common	vasodilatation

Uncommon	circulatory disorders (such as hypotension or rarely even circulatory collapse), flushing, hypertension*, orthostatic hypotension

Very Common	≥ 10%
Common	≥ 1% and < 10%
Uncommon	≥ 0.1% and < 1%
Rare	≥ 0.01% and < 0.1%
Very rare	< 0.01% including isolated reports

*at least one serious case

The incidence of adverse events did not vary with age or race. The incidence of most adverse events was similar for males and females, but females reported nausea, vomiting, dizziness and headache 10% to 15% more frequently than males.

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 BUPREDERMAL treatment. Instruct patients to promptly report the development of severe application site reactions and discontinue therapy.

Anaphylactic/Allergic Reactions

Cases of acute and chronic hypersensitivity to buprenorphine have been reported uncommonly both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to the use of BUPREDERMAL.

DOSAGE AND ADMINISTRATION

For application to the skin (transdermal use) only over 7 days.

Adults

The lowest dose, BUPREDERMAL patch 5 micrograms per hour, should be used as the initial dose. Consideration should be given to the previous opioid history of the patient, including opioid tolerance, if any, as well as current general condition and medical status of the patient. A maximum total dose of 40 micrograms per hour BUPREDERMAL should not be exceeded. No dosage adjustment is necessary in the elderly.

Titration

Discontinue all other around-the-clock opioid drugs when BUPREDERMAL therapy is initiated.During initiation and titration with BUPREDERMAL patch, patients should take the usual recommended doses of short-acting supplemental analgesics as needed until analgesic efficacy with BUPREDERMAL patch is attained.

The dose of BUPREDERMAL patch should not be increased at less than 3-day intervals when steady state levels are attained and the maximum effect of a given dose is established. Changes in BUPREDERMAL patch dosage may be individually titrated based on the need for supplemental when necessary (PRN) analgesia and the patient's response to BUPREDERMAL patch.

To increase the dose, the patch that is currently being worn should be removed and a higher strength of BUPREDERMAL patch or a combination of patches should be applied at a

different skin site to achieve the required dose. **A new patch should not be applied to the same skin site for three to four weeks**. It is recommended that no more than two patches be applied at the same time, up to a maximum of 40 microgram/hr BUPREDERMAL. If a 40 microgram patch is applied, no additional patches should be applied.

Patients should be carefully and regularly monitored to assess the optimum dose and duration of treatment. Titration should continue every three to seven days until adequate analgesia and improvement in function is achieved. If adequate pain relief cannot be achieved with maximal doses of BUPREDERMAL patch, the patient should be converted to an around-the-clock strong opioid.

Opioid-naïve patients

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 BUPREDERMAL patch is an appropriate opioid product. The lowest dose available (BUPREDERMAL patch 5 micrograms per hour) should be used as the initial dose. If the patient is taking supplemental analgesics, these may be continued on a PRN basis as the dose of BUPREDERMAL patch is adjusted.

Conversion from opioid or fixed-ratio opioid/non-opioid combination drugs

BUPREDERMAL patches have been used as an alternative in patients taking lower doses of opioids (up to 90 mg of oral morphine equivalents a day) and combination analgesics. Such patients should be started on a low dose of BUPREDERMAL patch and continue with the same dose and dosing scheduling of their previous daily regimen during titration.

Children

Use in children is not recommended due to lack of clinical safety and efficacy data in patients under 18 years of age.

Renal and hepatic impairment

No dosage adjustment is required in patients with renal impairment or mild to moderate hepatic impairment. Patients with severe hepatic impairment may accumulate buprenorphine and BUPREDERMAL patch should be used with caution, if at all, in such patients.

Discontinuation

During chronic therapy, periodically reassess the continued need for opioid analgesics. After removal of a BUPREDERMAL patch, buprenorphine serum concentrations decrease gradually, and the analgesic effect is maintained for a certain amount of time. This needs to be considered when use of BUPREDERMAL patch 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 BUPREDERMAL patch.

When the patient no longer requires therapy with BUPREDERMAL, use a gradual downward titration of the dose every 7 days to prevent signs and symptoms of withdrawal in the physically dependent patient; consider introduction of an appropriate immediate-release opioid medication. Do not abruptly discontinue BUPREDERMAL.

Method of application

BUPREDERMAL patches should be applied to non-irritated, intact skin of the upper outer arm, upper chest, upper back or the side of the chest, but not to any parts of the skin with large scars. Application sites should be rotated whenever a patch is replaced or added.

Application sites should be re-used at no less than three-week intervals. BUPREDERMAL patches should be applied to a relatively hairless or nearly hairless skin site. If none are available, the hair at the site should be cut with scissors, not shaven.

If the application site must be cleaned, it should be done with clean water only. Soaps, alcohol, oils, lotions or abrasive devices should not be used. The skin should be dry before the patch is applied. BUPREDERMAL patches should be applied immediately after removal from the sealed pouch packaging. Following removal of the release liner, the 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, they may be taped down with suitable skin tape. The patch should be worn continuously for 7 days.

Bathing, showering, or swimming should not affect the patch. If a patch falls off, a new one should be applied.

While wearing the BUPREDERMAL patch patients should be advised to avoid exposing the application site to direct external heat sources, such as heating pads, electric blankets, heat lamps etc. as an increase in the absorption of buprenorphine may occur. The effects of use in hot tubs and sauna have not been studied.

When changing a patch, patients should be instructed to remove the used BUPREDERMAL patch, fold it over on itself (bringing the adhesive sides together) and dispose of safely, out of reach of children.

OVERDOSAGE

Symptoms of overdose

Symptoms similar to other centrally acting analgesics are to be expected and are an extension of the pharmacological actions. These include respiratory depression including apnoea, sedation, drowsiness, nausea, vomiting, cardiovascular collapse and marked miosis although respiratory depression has been absent in some cases of buprenorphine overdosage.

Treatment of overdose

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

A specific opioid antagonist, such as naloxone, may reverse the effects of buprenorphine although naloxone may be less effective in reversing the effects of buprenorphine than other mu-agonists. Treatment with continuous intravenous naloxone should begin with the usual doses but high doses may be required. The onset of naloxone's effect may be delayed by 30 minutes or more. Please refer to naloxone hydrochloride injection product information for further information. There are literature which suggests that the dose response of buprenorphine-induced respiratory depression to treatment with naloxone is bell shaped with higher doses of naloxone providing less effective treatment of respiratory depression than intermediate ones. Maintenance of adequate ventilation is more important than treatment with naloxone.

Please phone the Poisons Information Centre on 13 11 26 for advice on managing overdose.

PRESENTATION AND STORAGE CONDITIONS

BUPREDERMAL® transdermal drug delivery system is a rectangular or square, beige-coloured transdermal matrix patch with rounded corners. Available in seven strengths:

BUPREDERMAL® patch 5
Each square patch releases buprenorphine 5 micrograms per hour.
The area containing the active substance: 6.25 cm^2
Total buprenorphine content: 5 mg

BUPREDERMAL® patch 10
Each rectangular patch releases buprenorphine 10 micrograms per hour.
The area containing the active substance: 12.5 cm^2
Total buprenorphine content: 10 mg

BUPREDERMAL® patch 15*
Each rectangular patch releases buprenorphine 15 micrograms per hour.
The area containing the active substance: 18.75 cm^2
Total buprenorphine content: 15 mg

BUPREDERMAL® patch 20
Each square patch releases buprenorphine 20 micrograms per hour.
The area containing the active substance: 25 cm^2
Total buprenorphine content: 20 mg

BUPREDERMAL® patch 25*
Each rectangular patch releases buprenorphine 25 micrograms per hour.
The area containing the active substance: 31.25 cm^2
Total buprenorphine content: 25 mg

BUPREDERMAL® patch 30*
Each rectangular patch releases buprenorphine 30 micrograms per hour.
The area containing the active substance: 37.5 cm^2
Total buprenorphine content: 30 mg

BUPREDERMAL® patch 40*
Each rectangular patch releases buprenorphine 40 micrograms per hour.
The area containing the active substance: 50 cm^2
Total buprenorphine content: 40 mg

Each BUPREDERMAL® patch is printed with the trade name and the strength in blue ink.
BUPREDERMAL® patch 5, 10 and 20 is supplied in cartons containing one*, two or four* individually packaged patches.
BUPREDERMAL® patch 15, 25, 30 and 40 is supplied in cartons containing two* or four* individually packaged patches.

* Not all of strengths and pack sizes are currently marketed in Australia.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Mundipharma Pty Limited
ABN 087 081 322 509
88 Phillip Street
SYDNEY, NSW 2000

Further information may be obtained from Mundipharma's Medical Information Department 1800 188 009.

POISON SCHEDULE OF THE MEDICINE

S8

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

07 September 2017

DATE OF MOST RECENT AMENDMENT

29 November 2017

® BUPREDERMAL is a registered trade mark.

Orbis AU-4163