

NORSPAN® TRANSDERMAL PATCH

Buprenorphine 5, 10 or 20µg/hr

Presentation

NORSPAN® patches are either rectangular (10 micrograms/hr) or square (5 and 20 micrograms/hr) 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 foil over the adhesive matrix; (4) the buprenorphine-containing adhesive matrix; and (5) a release liner. Before use the release liner covering the adhesive layer is removed and discarded.

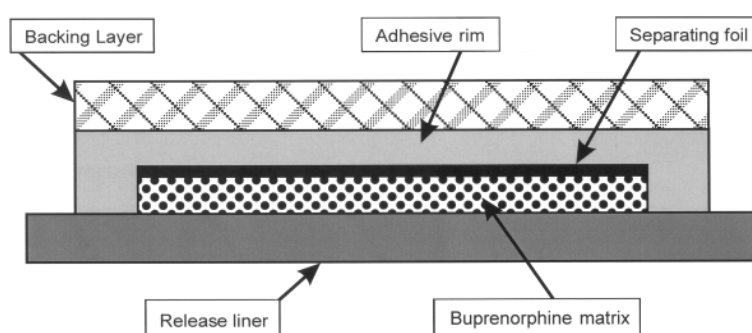


Figure 1: Cross section drawing of NORSPAN® patch

NORSPAN® transdermal system is available in three different strengths: 5 micrograms/hr, 10 micrograms/hr and 20 micrograms/hr. The composition of all three strengths is identical except for 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 system. The skin is the limiting barrier to diffusion from the system into the bloodstream.

Uses**Actions**

Buprenorphine is a partial opioid agonist, acting at the mu opioid receptor. It also has antagonistic activity at the kappa opioid receptor. The opioid agonist activities of buprenorphine are dose related.

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 medicine.

Buprenorphine produces similar effects to other opioids on the central nervous system, and the cardiovascular, 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

medicines 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. NORSPAN[®] patch application resulted in transient decreases in blood pressure in healthy young and elderly subjects, without clinical adverse events.

Respiratory depression is less common than with full mu-agonists, such as morphine, and there appears to be a ceiling effect. When respiratory depression occurs it appears to have a slower onset and longer duration compared to morphine.

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 semisynthetic opioid, has immunological effects similar to morphine.

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

Pharmacokinetics

Each NORSPAN[®] patch provides a steady delivery of buprenorphine for up to seven days. Steady state is achieved by day 3 following the first application. After removal of NORSPAN[®] patch buprenorphine concentrations decline, decreasing approximately 50% in 12 hours (range 10-24h).

NORSPAN[®] patches 5 micrograms/hr, 10 micrograms/hr and 20 micrograms/hr provide dose-proportional increases in total exposure (AUC) over the 7-day application period. Dose proportional increases in plasma concentrations occur at steady state with NORSPAN[®] 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 NORSPAN[®] patch 5 micrograms/hr releases 5 micrograms of buprenorphine per hour, and contains a total of 5mg of buprenorphine. Each NORSPAN[®] patch 10 micrograms/hr releases 10 micrograms of buprenorphine per hour and contains a total of 10mg of buprenorphine. Each NORSPAN[®] patch 20 micrograms/hr releases 20 micrograms of buprenorphine per hour and contains a total of 20mg of buprenorphine.

Absorption

Following NORSPAN[®] patch application, buprenorphine diffuses from the patch through the skin. In clinical pharmacology studies, the median time for NORSPAN[®] patch 10 micrograms/hr to deliver detectable buprenorphine concentrations (25 picograms/mL) was approximately 17 hours. The bioavailability of buprenorphine from a NORSPAN[®] patch relative to IV is 15% (for all three strengths).

Accidental oral ingestion: measurable systemic levels of buprenorphine were demonstrated in dogs given NORSPAN[®] 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 430L, which is indicative of the high lipophilicity of the medicine. 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 NORSPAN[®] 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 2 primary metabolites, norbuprenorphine and buprenorphine 3-O-glucuronide, respectively. Norbuprenorphine is also glucuronidated prior to elimination. Buprenorphine is also eliminated in the faeces within 7 days.

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

Norbuprenorphine is the only known active metabolite of buprenorphine. It has been shown to be a respiratory depressant in rats at concentration at least 50-fold those seen following application of NORSPAN[®] patch 20 micrograms/hr.

Specific inhibitors of CYP450 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of the buprenorphine metabolite, norbuprenorphine, in human microsomes.

Application Site

A study in healthy subjects demonstrated that the pharmacokinetic profile of buprenorphine delivered by NORSPAN[®] 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 NORSPAN[®] 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 NORSPAN[®] patch caused a transient, 26-55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed. For this reason, applying heat sources such as hot water bottles, heat pads or electric blankets directly to the NORSPAN[®] patch is not recommended. A heating pad applied to a NORSPAN[®] patch site directly after patch removal did not alter absorption from the skin depot.

Clinical Trials

The safety and efficacy of NORSPAN[®] patches in the management of chronic pain has been studied in 10 clinical trials [1,698 patients treated with NORSPAN[®] 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 NORSPAN[®] 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 NORSPAN[®] patches 5, 10 and 20mg applied every 7 days with sublingual buprenorphine tablets 200 and 400mcg [Temgesic] in 238 patients with moderate to severe pain due to osteoarthritis [hip and/or knee, 85% >1 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 3 and 7, BS-11 scale]. The Per Protocol 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 0.001-0.13]. 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 – demonstrating equivalent efficacy. At study completion 70% [40/51] of patients on patch and 75% [42/51] on tablets rated their pain relief as good or very

good.

	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 400mcg 6-8 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% NORSPAN[®] 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 NORSPAN[®] patches 5, 10 and 20mg, applied every 7 days, with hydrocodone/paracetamol [2.5mg/250mg] tablets qid in 270 patients with chronic moderate to severe back pain [pain intensity ≥ 5], not controlled by non-opioid analgesia alone [ibuprofen 400mg 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[†]. The Intent to Treat mean baseline pain intensity was 7.74 (NORSPAN[®] 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, 0.44]. The difference between the two treatments in patient global satisfaction was 0.16 [-0.08, 0.39]. NORSPAN[®] patches were equally effective to hydrocodone/paracetamol tablets in relieving pain and for patient satisfaction.

	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 NORSPAN[®] 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.

Dosage and Administration

For transdermal use over 7 days.

Adults

The lowest dose, NORSPAN[®] patch 5 micrograms/hr 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. No dosage adjustment is necessary in the elderly.

Titration

During initiation and titration with NORSPAN[®] patch, patients should take the usual recommended doses of short-acting supplemental analgesics as needed until analgesic efficacy with NORSPAN[®] patch is attained.

The dose of NORSPAN[®] 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 NORSPAN[®] patch dosage may be individually titrated based on the need for supplemental PRN analgesia and the patient's response to NORSPAN[®] patch.

To increase the dose, the patch that is currently being worn should be removed and a higher strength of NORSPAN[®] 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 3-4 weeks.** It is recommended that no more than two patches be applied at the same time, regardless of strength.

Patients should be carefully and regularly monitored to assess the optimum dose and duration of treatment. If adequate pain relief cannot be achieved with maximal doses of NORSPAN[®] 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 NORSPAN[®] patch is an appropriate opioid product. The lowest dose available (NORSPAN[®] patch 5 micrograms/hr) 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 NORSPAN[®] patch is adjusted.

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

NORSPAN[®] patches have been used as an alternative in patients taking lower doses of opioids (up to 90mg of oral morphine-equivalents a day) and combination analgesics. Such patients should be started on a low dose of NORSPAN[®] patch and continue with the same dose and dosing scheduling of their previous daily regimen basis 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 NORSPAN[®] patch should be used with caution, if at all, in such patients.

Discontinuation

After the removal of a NORSPAN[®] 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 NORSPAN[®] 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 NORSPAN[®] patch.

Method of Application

NORSPAN[®] 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. NORSPAN[®] 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. NORSPAN[®] patches should be applied immediately after removal from the sealed pouch packaging. Following removal of the release liner, the transdermal patch should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure the contact is complete, especially around the edges. If the edges of the patch begin to peel off, 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 NORSPAN[®] patch patients should be advised to avoid exposing the application site to external heat sources, such as heating pads, electric blankets, heat lamps, saunas, hot tubs and heated water beds, etc, as an increase in the absorption of buprenorphine may occur. The effects of use in hot tubs and sauna has not been studied.

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

Application sites should be rotated whenever a system is replaced or added. A new patch should not be applied to the same skin site for 3-4 weeks.

Contraindications

NORSPAN[®] patches are contraindicated in patients with known hypersensitivity to buprenorphine or any components of the patch.

NORSPAN[®] patches are contraindicated in patients with severely impaired respiratory function and in patients concurrently receiving non-selective monoamine oxidase inhibitors (MAOI's) or within 14 days of stopping treatment with non-selective MAOI's.

NORSPAN[®] patches must not be used for the treatment of opioid dependence and narcotic withdrawal.

Warnings and Precautions

NORSPAN[®] 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, or in patients with severe hepatic impairment. 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 opioid preparations, patients who are to undergo cordotomy or other pain relieving surgical procedures should not use NORSPAN[®] patches for at least 24 hours prior to surgery. NORSPAN[®] patches should be used with caution following abdominal surgery, as opioids are known to impair intestinal motility.

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. Additional overdosage deaths due to ethanol and benzodiazepines in combination with buprenorphine have been reported. Caution should be exercised when prescribing NORSPAN[®] patches to patients known to have, or suspected of having, problems with drug or alcohol abuse or serious mental illness.

In a study of the effect of NORSPAN[®] patches on the QTc interval in 131 healthy males, therapeutic dosages (10mcg/h) had no effect on the QTc interval. Higher dosages (40mcg/h) and the active control (moxifloxacin 400mg) each produced increases of 5.9 msec in the QTc interval. This observation should be considered when prescribing NORSPAN[®] patches for patients with congenital QT prolongation and for patients taking antiarrhythmic medications in either Class 1A (e.g. quinidine, procainamide) or in Class III (e.g. amiodarone, sotalol) or any other medication which prolongs the QT interval.

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, patients with severe febrile illness should be monitored for side effects and may require dose adjustment.

As with all opioids, a reduction in dosage may be advisable in hypothyroidism.

NORSPAN[®] 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.

Drug Dependence

Controlled human and animal studies indicate that buprenorphine has a lower dependence liability than pure agonist analgesics. In man limited euphorogenic effects have been observed with buprenorphine. This may result in some abuse of the product and caution should be exercised when prescribing to patients known to have, or suspected of having a history of drug abuse.

Chronic use of buprenorphine can result in the development of physical dependence. Withdrawal (abstinence syndrome), when it occurs, is generally mild, begins after 2 days and may last up to 2 weeks.

Use in Narcotic Dependent Patients

Physicians should be careful not to prescribe NORSPAN[®] patches for known or suspected narcotic dependent patients. Due to its antagonist properties, NORSPAN[®] patches may not substitute for other opioid agonists and may induce withdrawal symptoms in these patients.

Opioid Naïve Patients

The lowest dose available, NORSPAN[®] patch 5 micrograms/hr, 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 NORSPAN[®] patch treatment. Consideration should be given to alternative therapy and NORSPAN[®] patches should be used with caution, if at all, in such patients.

Use in Children

The safety and efficacy of NORSPAN[®] patches in patients under 18 years of age has not been established.

Driving and Operating Dangerous Machinery

NORSPAN[®] transdermal 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, tranquillisers, sedatives and hypnotics. If affected, patients should not drive or operate machinery for at least 24 hours after the NORSPAN[®] patch has been removed.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Carcinogenesis and genotoxicity

The carcinogenic potential of buprenorphine is currently unknown.

No carcinogenicity studies of NORSPAN[®] patches have been conducted. No evidence for carcinogenicity due to buprenorphine was noted in life time studies in mice at PO doses up to 100mg/kg/day. In rats, however, an increased incidence of testicular tumours was observed at doses greater than 5.5mg/kg/day. The no-effect level in both studies are at least 80 times greater than the expected daily systemic dose of buprenorphine in humans during treatment with NORSPAN[®] patch 20mg, on a surface area basis.

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.

Impairment of fertility

Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily PO doses up to 80mg/kg/day or daily SC doses up to 5mg/kg/day. These doses are at least 75 times greater than the expected daily systemic dose of buprenorphine in humans during treatment with NORSPAN[®] patch 20mg, on a surface area basis.

Use in Pregnancy

Category C.

Buprenorphine has been shown to cross the placenta. 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 medicines. There are no adequate and well-controlled studies of buprenorphine or NORSPAN[®] patches in pregnant women.

In pregnant rabbits, buprenorphine produced statistically significant pre-implantation losses at PO doses \geq 1mg/kg/day and post-implantation losses at IV doses \geq 0.2mg/kg/day (medicine

exposure in animals about 6 times the expected daily systemic dose of buprenorphine in humans during treatment with NORSPAN[®] patches 20mg, on a surface area basis). Dystocia was noted in pregnant rats treated IM with buprenorphine doses > 1mg/kg/day (approximately 17 times the expected human daily dose during treatment with NORSPAN[®] patches 20mg). Fertility and peri- and post-natal development studies with buprenorphine in rats showed increases in neonatal mortality after doses of 0.8mg/kg/day PO, 0.5mg/kg/day IM or 0.1mg/kg/day SC (approximately 14, 9 and 1.7 times, respectively, the human daily dose during treatment with NORSPAN[®] patch 20mg on a mg/m² basis). No-effect doses for neonatal mortality were not established. Delays in the occurrence of righting reflex and startle response were noted in rat pups at a buprenorphine dose > 8mg/kg/day PO (> 100 times the expected human daily dose during treatment with NORSPAN[®] patch 20mg on a mg/m² basis). No evidence for teratogenic activity was observed in animal studies at buprenorphine doses ranging from 14 to > 100 times the expected human daily dose during treatment with NORSPAN[®] patch 20mg, on a surface area basis).

No effects on embryofetal development were noted in studies with topically applied NORSPAN[®] patches in rats and rabbits (systemic exposure to buprenorphine up to about 30 and 6 times, respectively, the expected human daily dose during treatment with NORSPAN[®] patch 20mg, on a surface area basis). However, systemic absorption was demonstrated only during late gestation in rabbits.

Use in Lactation

Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. Decreases in post-natal survival, growth and development were also observed in animals treated with buprenorphine during lactation. Because buprenorphine passes into mother's milk, NORSPAN[®] patches should not be used by breastfeeding women.

Adverse Effects

Adverse reactions that may be associated with NORSPAN[®] 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.

In general, included adverse events are those with a plausible relation to drug use, and excluded adverse events are minor events, those that are too imprecise to be meaningful, and events that may be commonly observed in the absence of drug therapy.

The frequencies are given as follows:

Very common:	≥ 10%
Common:	≥ 1%, < 10%
Uncommon:	≥ 0.1%, < 1%
Rare:	≥ 0.01%, < 0.1% (isolated cases)
Very rare:	≤ 0.001% including isolated reports
*	At least one serious case

Immune system disorders

Uncommon: allergic reaction (including oropharyngeal swelling and swollen tongue)

Metabolism and nutrition disorders

Common: anorexia
Uncommon: dehydration

Psychiatric disorders

Common: confusion, depression, insomnia, nervousness
Uncommon: affect lability, agitation, anxiety, de-personalisation, euphoric mood, hallucination, libido decreased, nightmare

Rare: psychotic disorder

Nervous system disorders

Very common: dizziness, somnolence*

Common: anxiety, confusion, depression*, insomnia, nervousness, paraesthesia

Uncommon: affect lability, agitation, concentration impairment, co-ordination abnormal, depersonalization, dysarthria, dysgeusia, euphoric mood, hallucination, hypoaesthesia, libido decreased, memory impairment, migraine, nightmare, restlessness, sedation, sleep disorder, syncope*, tremor

Rare: dysequilibrium, numbness, psychotic disorder

Very rare: dependence, mood swings, muscle fasciculation

Eye disorders

Uncommon: dry eye, vision blurred

Rare: miosis, eyelid oedema, visual disturbance

Ear and labyrinth disorders

Uncommon: tinnitus, vertigo

Very rare: ear pain

Cardiovascular disorders

Common: vasodilatation

Uncommon: angina pectoris, circulatory disorders (such as hypotension or rarely even circulatory collapse), flushing, hypertension*, orthostatic hypotension, palpitations, tachycardia

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea*

Uncommon: asthma aggravated*, cough, hiccups, hyperventilation, hypoxia, rhinitis*, wheezing*

Rare: respiratory failure*, respiratory depression

Gastrointestinal disorders

Very common: constipation*, dry mouth, nausea*, vomiting*

Common: abdominal pain*, diarrhoea*, dyspepsia*, anorexia

Uncommon: flatulence

Rare: diverticulitis*, dysphagia, ileus, biliary colic*, pyrosis (heartburn)

Very rare: retching

Hepatobiliary disorders

Rare: biliary colic*

Skin and subcutaneous tissue disorders

Very common: application site reaction, pruritus*, pruritus at site

Common: erythema at site, exanthema, rash*, rash at site, sweating*

Uncommon: dry skin, face oedema, urticaria, dermatitis contact**

Rare: local allergic reactions with marked sign of inflammation (in such cases, discontinue NORSPAN® transdermal patch)

Very rare: pustules, vesicles

Musculoskeletal and connective tissue disorders

Uncommon: muscle cramp, muscle spasm, myalgia

Renal and urinary disorders

Uncommon: urinary incontinence, urinary retention

Rare: urinary hesitation

Reproductive system and breast disorders

Rare: sexual dysfunction, decreased erection

General disorders and administration site conditions

Very common: application site reaction+

Common: asthenic conditions*, (including muscle weakness), chest pain*, pain, peripheral oedema

Uncommon: influenza-like illness, oedema, pyrexia*, rigors*, withdrawal syndrome, application site dermatitis+

Investigations

Uncommon: alanine aminotransferase increased, weight decreased

Injury, poisoning and procedural complications

Uncommon: accidental injury (including fall)

Body as a whole

Very common: headache*

Common: abdominal pain*, asthenia* (including muscle weakness), chest pain*, pain oedema, peripheral oedema, tiredness

Uncommon: accidental injury (including fall), allergic reaction (including oropharyngeal swelling and swollen tongue), influenza-like illness, malaise, muscle cramp, muscle spasm, myalgia, pyrexia*, rigors*, withdrawal syndrome

Very rare: serious allergic reactions

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.

+ Includes: application site erythema, application site oedema, application site pruritus, application site rash

** In some cases late onset local allergic reactions occurred with marked signs of inflammation. In such cases treatment with NORSPAN[®] patches should be terminated.

Interactions

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

NORSPAN[®] patches, like all opioid analgesics, should be dosed with caution in patients who are currently taking other CNS depressants or other drugs that may cause respiratory depression, hypotension, profound sedation or potentially result in coma. Such agents include sedatives or hypnotics, general anaesthetics, other opioid analgesics, phenothiazines, centrally acting anti-emetics, benzodiazepines and alcohol.

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.

Buprenorphine is metabolised to norbuprenorphine by CYP450 3A4. Caution is advised when NORSPAN[®] patches are administered concurrently with inhibitors of CYP3A4 (e.g. protease inhibitors, some medicine classes ofazole antimycotics, calcium channel antagonists and macrolide antibiotics) as this may lead to increased levels of buprenorphine. The interaction

between buprenorphine and CYP3A4 enzyme inducers has not been studied. Co-administration of NORSPAN[®] patches and enzyme inducers (e.g. phenobarbitone, carbamazepine, phenytoin, rifampicin) could lead to increased clearance resulting in reduced efficacy.

In clinical trial patients there were no apparent effects on NORSPAN[®] patch exposure when used concomitantly with various H₂-antagonists or proton pump inhibitors.

Medicine/Laboratory Test Interactions

Increased aminotransferase levels and weight decrease have been noted.

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. Respiratory depression has been absent in some cases of 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 μ -opioid agonists. Treatment with continuous intravenous naloxone should begin with the usual doses but high doses may be required..

Pharmaceutical Precautions

Store below 25°C.

Medicine Classification

Controlled Drug C4.

Package Quantities

Rectangular or square, beige coloured transdermal matrix patches with rounded corners. Available in three different strengths/sizes:

NORSPAN[®] patch 5

Each patch releases buprenorphine 5 micrograms/hr

The area containing the active substance: 6.25 cm²

Total buprenorphine content: 5mg

NORSPAN[®] patch 10

Each patch releases buprenorphine 10 micrograms/hr

The area containing the active substance: 12.5 cm²

Total buprenorphine content: 10mg

NORSPAN[®] patch 20

Each patch releases buprenorphine 20 micrograms/hr
The area containing the active substance: 25 cm²
Total buprenorphine content: 20mg

Each NORSPAN[®] patch is printed with the trade name and the strength in blue ink. NORSPAN[®] patch is supplied in cartons containing 2 individually packaged patches.

Further Information

Buprenorphine base (active). CAS Registry Number 52485-79-7.

The inactive ingredients in NORSPAN[®] transdermal patches are levulinic acid, oleyl oleate, povidone, Duro Tak 387-2051, Duro Tak 387-2054 and polyethylene terephthalate.

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, 5 α -epoxy-3-hydroxy-6-methoxy-6 α , 14-ethano-14 α -morphinan-7 α -yl]-3, 3-dimethylbutan-2-ol. The molecular weight is 467.6 and the empirical formula is C₂₉H₄₁NO₄.

Name and Address

Distributed on behalf of Mundipharma New Zealand Limited by:
Pharmaco (N.Z.) Ltd
P O Box 4079
AUCKLAND
Ph: (09) 377-3336
Toll Free [Medical Enquiries]: 0800 773 310

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