NORSPAN® TRANSDERMAL PATCH

Buprenorphine

1 PRODUCT NAME

NORSPAN® 5mg Patch
NORSPAN® 10mg Patch
NORSPAN® 20mg Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NORSPAN® patch 5
Each square patch releases buprenorphine 5 micrograms per hour over 7 days
The area containing the active substance: 6.25 cm^2
Total buprenorphine content: 5mg

NORSPAN® patch 10
Each rectangular patch releases buprenorphine 10 micrograms per hour over 7 days
The area containing the active substance: 12.5 cm^2
Total buprenorphine content: 10mg

NORSPAN® patch 20
Each square patch releases buprenorphine 20 micrograms per hour over 7 days
The area containing the active substance: 25 cm^2
Total buprenorphine content: 20mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

NORSPAN® patch is 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 layer ("foil") consisting of polyethylene terephthalate 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.

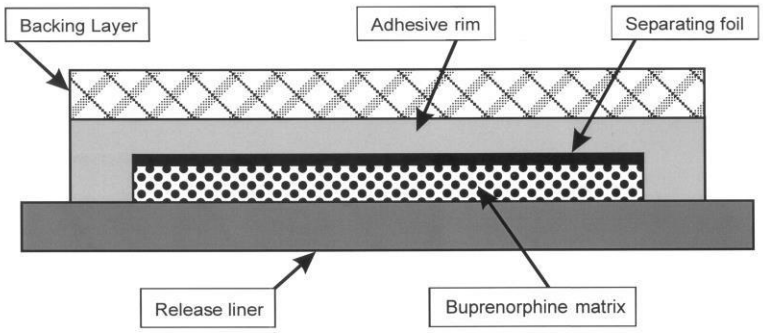


Figure 1: Cross section drawing of NORSPAN® patch

NORSPAN® patch is available in three different strengths: 5 micrograms per hour, 10 micrograms per hour and 20 micrograms per hour. The composition of all three 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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of moderate to severe pain.

4.2 Dose and method of administration

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

Adults

The lowest dose, NORSPAN® 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. No dosage adjustment is necessary in the elderly.

Titration

Discontinue all other around-the-clock opioid drugs when NORSPAN® patch is initiated.
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.

During the titration process, the dose may be adjusted every 3-days (72 hours). Thereafter, the 7-day dosing interval should be maintained. Changes in NORSPAN® patch dosage may be individually titrated based on the need for supplemental when necessary (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 three weeks. It is recommended that no more than two patches be applied at the same time, up to a maximum total dose of 40 micrograms/hr.

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 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 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 NORSPAN® patch is adjusted.

Conversion from Opioid or Fixed Ratio Opioid/Non-Opioid Combination Medicines
NORSPAN® patch has 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 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
During chronic therapy, periodically reassess the continued need for opioid analgesics. 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.

When the patient no longer requires therapy with NORSPAN® patch, 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 NORSPAN® patch.

Method of Application
In order to ensure effective analgesia of buprenorphine and to minimise the potential of skin reactions (see section 4.4), the following directions of use should be followed:

NORSPAN® patch 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 system is replaced or added. A new patch should not be applied to the same application site for 3 weeks. NORSPAN® patch 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® patch 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 NORSPAN® patch patients should be advised to avoid exposing the application site to direct external heat sources, such as heating pads, electric blankets, hot water bottles, heat lamps, 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.

4.3 Contraindications

NORSPAN® patch is contraindicated in patients with known hypersensitivity to buprenorphine or any components of the patch (see Section 6.1), including previous history of application site reactions suggestive of allergic contact dermatitis with buprenorphine transdermal patches, myasthenia gravis, delirium tremens and pregnancy.

NORSPAN® patch is 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.

NORSPAN® patch must not be used for the treatment of opioid dependence and opioid withdrawal.

4.4 Special warnings and precautions for use

NORSPAN® should be used with caution in patients with:

- Severely impaired respiratory function
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Serotonergic agents (see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Psychological dependence (addiction), abuse profile and history of substance and/or
- Alcohol abuse (see below)
- Head injury, intracranial lesions or increased intracranial pressure, shock, a reduced level of consciousness of uncertain origin
- Severely impaired hepatic function (see section 4.2)
- Constipation

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 dose may be advisable in hypothyroidism.

Respiratory depression

The primary risk of opioid excess is respiratory depression.
Opioids may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent manner in some patients. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

CNS depressants co-administration

Concomitant use of NORSPAN® and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe opioids concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. It is unknown if such severity can be expected from transdermal formulation of buprenorphine.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see Section 4.5 Interactions with other medicines and other forms of interaction).

Advise both patients and caregivers about the risks of respiratory depression and sedation when NORSPAN® patch is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see Section 4.5 Interactions with other medicines and other forms of interaction).

Serotonin syndrome

Concomitant administration of buprenorphine and other serotonergic agents, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Tolerance, physical dependence and withdrawal
Buprenorphine is a μ-opioid agonist.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this NORSPAN® may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy.

When a patient no longer requires therapy with buprenorphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. If NORSPAN® patch 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).

Administration of buprenorphine to persons who are physically dependent on full μ-opioid agonists may precipitate an abstinence syndrome depending on the level of physical dependence, and the timing and dose of buprenorphine.

Psychological dependence (addiction), abuse profile and history of substance and/or alcohol abuse

There is potential for development of psychological dependence (addiction) to opioid analgesics, including buprenorphine. Buprenorphine has an abuse profile similar to other opioids.
Buprenorphine may be sought and abused by people with latent or manifest addiction disorders.
NORSPAN® should be used with particular care in patients with a history of substance misuse disorder (including alcohol misuse) or mental health disorder.

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

Although the risk of addiction in any individual is unknown, it may occur in patients appropriately prescribed NORSPAN® patch 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 NORSPAN® patch and monitor all patients receiving NORSPAN® patch 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.

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

NORSPAN® patch 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 Section 4.9 OVERDOSAGE).

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. NORSPAN® patch should be ceased if there is any evidence of misuse or abuse, or if NORSPAN® patch is having a detrimental effect.

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

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.

Use in patients with seizures
Buprenorphine may lower the seizure threshold in patients with a history of seizure disorder.

Hyperalgesia
Hyperalgesia that will not respond to a further dose increase of buprenorphine may occur in particular in high doses. A dose reduction or change in opioid may be required.

Opioid-Naïve Patients
The lowest dose available, NORSPAN® 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 NORSPAN® patch treatment. Consideration should be given to alternative therapy and NORSPAN® patch should be used with caution, if at all, in such patients.

Effect on laboratory tests
Increased alanine aminotransferase levels.

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, hot water bottles 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.

Skin reactions at application site

To minimise the risk of occurrence of application site skin reactions, it is important to follow the posology instructions (see section 4.2).

Application site reactions with NORSPAN® are usually presented by a mild or moderate skin inflammation (contact dermatitis), and their typical appearance may include erythema, oedema, pruritus, rash, small blisters (vesicles), and painful/burning sensation at the application site. Most commonly the cause is skin irritation (irritant contact dermatitis), and these reactions resolve spontaneously after NORSPAN® removal.

NORSPAN® may also cause skin sensitisation and subsequent allergic contact dermatitis (immune-mediated, type IV hypersensitivity reaction). Allergic contact dermatitis may develop with a significant delay (it may take months after NORSPAN® treatment initiation), and may manifest with symptoms similar to irritant contact dermatitis, or with more intense symptoms, such as "burn"-like lesions with bullae and discharge, which may spread outside the application site and which may not resolve rapidly after NORSPAN® removal. Patients and caregivers should be instructed accordingly to monitor the application sites for such reactions. If allergic contact dermatitis is suspected, relevant diagnostic procedures should be performed to determine if sensitisation has occurred and its actual cause (buprenorphine and/or other ingredients of the patch). If allergic contact dermatitis has been confirmed, treatment should be discontinued (see section 4.3). Continued NORSPAN® treatment in individuals experiencing allergic contact dermatitis may lead to complications, including blistering of the skin, open wound, bleeding, ulceration, and subsequent infections. Mechanical injuries during patch removal (e.g. laceration) are also possible in patients with fragile skin. Chronic inflammation may lead to long-lasting sequelae, such as post-inflammatory hyper- and hypopigmentation, as well as dry and thick scaly skin lesions, which may closely resemble scars.

Use in Children
The safety and efficacy of NORSPAN® patch in patients under 18 years of age has not been established.

4.5 Interaction with other medicines and other forms of interaction

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

Benzodiazepines and other Central Nervous System (CNS) depressants

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).
Such agents include sedatives or hypnotics, general anesthetic's, other opioid analgesics, phenothiazines, centrally acting anti-emetics, benzodiazepines and alcohol

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).

Buprenorphine is primarily metabolised by glucuronidation and to a lesser extent (about 30%) by CYP3A4. Concomitant treatment with CYP3A4 inhibitors may lead to elevated plasma concentrations with intensified efficacy of buprenorphine. A drug interaction study with the CYP3A4 inhibitor ketoconazole did not produce clinically relevant increases in mean maximum (Cmax) or total (AUC) buprenorphine exposure following NORSPAN® with ketoconazole as compared to NORSPAN® alone.

The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied; however, co-administration of NORSPAN® patch 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.

Patients receiving NORSPAN® with CYP3A4 inhibitors should be closely monitored.

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.

Serotonergic agents
It is unknown whether there is an interaction between selective MAOIs (e.g. selegiline) and buprenorphine, hence, caution is advised with this drug combination.
Buprenorphine should be used cautiously when co-administered with serotonergic medicinal products (e.g. SSRIs, SNRIs or tricyclic antidepressants), as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

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 NORSPAN® patch is used concurrently with anticholinergic drugs.

4.6 Fertility, pregnancy and lactation

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 medicines. 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 NORSPAN® patch in pregnant women.

In pregnant rabbits, buprenorphine produced statistically significant pre-implantation losses at PO doses ≥ 1mg/kg/day and post-implantation losses at intravenous (IV) doses ≥ 0.2mg/kg/day (medicine exposure in animals about 6 times the expected daily systemic dose of buprenorphine in humans during treatment with NORSPAN® patch 20mg, on a surface area basis). Dystocia was noted in pregnant rats treated intramuscular (IM) with buprenorphine doses > 1mg/kg/day (approximately 17 times the expected human daily dose during treatment with NORSPAN® patch 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® patch 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.

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.

Breastfeeding
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. Buprenorphine passes into mother's milk at low concentrations and therefore, NORSPAN® patch should not be used by breastfeeding women.

Fertility
No human data on the effect of buprenorphine on fertility are available. In animal studies, no effect on fertility has been observed with buprenorphine (see section 5.3)

4.7 Effects on ability to drive and use machines
NORSPAN® 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.

4.8 Undesirable 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.

The following adverse reactions have been reported:

Immune system disorders

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

Metabolism and nutrition disorders

Common	anorexia
Uncommon	dehydration*, weight decreased

Psychiatric disorders

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

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
Not Known	convulsions hyperalgesia sleep apnoea syndrome

Eye disorders

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

Ear and labyrinth disorders

Uncommon	tinnitus, vertigo
Very rare	ear pain

Cardiac disorders

Uncommon	angina pectoris, palpitations, tachycardia

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

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

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

Hepatobiliary disorders

Rare	billiary colic

Skin and subcutaneous tissue disorders

Very Common	pruritus*
Common	exanthema, rash*, sweating*
Uncommon	dry skin, face oedema, urticaria
Very rare	pustules, vesicles

Musculoskeletal and connective tissue disorders

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

Renal and urinary disorders

Uncommon	urinary incontinence, urinary retention
Rare	urinary hesitation

Reproductive system and breast disorders

Rare	decreased erection, sexual dysfunction

General disorders and administration site conditions

Very common	application site skin reaction † **
Common	asthenic conditions* (including muscle weakness, lethargy, fatigue and malaise), pain, peripheral oedema, tiredness
Uncommon	oedema, pyrexia*, rigors*, drug withdrawal syndrome, chest pain*,
Rare	influenza-like illness
Not known	Drug withdrawal syndrome neonatal Drug tolerance

Injury, poisoning and procedural complications

Uncommon	accidental injury (including fall)

Investigations

Uncommon	Alanine aminotransferase increased Weight decreased

Very Common	≥ 10%
Common	≥ 1% and < 10%
Uncommon	≥ 0.1% and < 1%
Rare	≥ 0.01% and < 0.1% (isolated cases)
Very rare	< 0.01%

* at least one serious case

†Include common signs and symptoms of contact dermatitis (irritative or allergic): erythema, oedema, pruritus, rash, vesicles, painful/burning sensation at the application site.

**In some cases late onset local allergic reactions (allergic contact dermatitis) occurred with marked signs of inflammation. In such cases treatment with NORSPAN® should be terminated (see sections 4.3 and 4.4).

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 NORSPAN® patch. 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 NORSPAN® patch.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

The manifestations of buprenorphine overdose are an extension of its pharmacologic actions. Respiratory depression has been absent in some cases of buprenorphine overdose. However, respiratory depression, including apnoea, has occurred in other overdose situations. Additional symptoms include sedation, drowsiness, nausea, vomiting, cardiovascular collapse and marked miosis.
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-agonists. Treatment with continuous intravenous naloxone should begin with the usual doses but high doses may be required.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800764766).

5 PHARMACOLOGICAL PROPERTIES

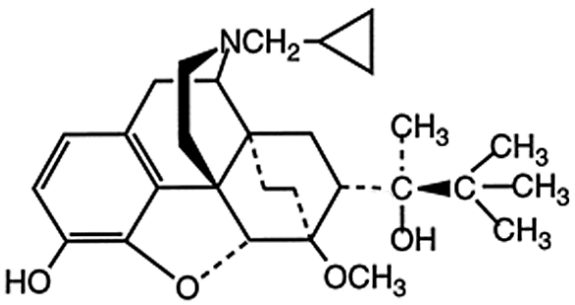
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, opioids

ATC code: N02 AE01

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

The structural formula is:



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 $C_{29}H_{41}NO_4$.

Buprenorphine is a μ-opioid agonist, acting at mu-opioid receptors. The opioid agonist activities of buprenorphine 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 medicine.

Buprenorphine produces similar effects to other opioids on the central nervous, 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.

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 semisynthetic opioid, has immunological effects similar to morphine.

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

Clinical Trials

The safety and efficacy of NORSPAN® patch in the management of chronic pain has been studied in 10 clinical trials [1,698 patients treated with NORSPAN® patch]. 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® patch 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® patch 5, 10 and 20mg applied every seven 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% >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 - see Table 1]. 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 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 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 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 seven days, with hydrocodone/paracetamol [2.5mg/250mg] tablets four times a day (qid) in 270 patients with chronic moderate to severe back pain [pain intensity ≥5 BS-11 scale], 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+, refer Table 2. The Intent to Treat (ITT) population 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 to 0.44]. The difference between the two treatments in patient global satisfaction was 0.16 [-0.08 to 0.39]. NORSPAN® patch was 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]

* 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"

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.

5.2 Pharmacokinetic properties

Each NORSPAN® 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 NORSPAN® patch buprenorphine concentrations decline, decreasing approximately 50% in 12 hours (range 10-24 hours).

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 per hour to deliver detectable buprenorphine concentrations (100 picograms/mL) was approximately 17 hours. The mean bioavailability of buprenorphine from a NORSPAN® patch relative to intravenous (IV) dosing is 15% (for all three strengths).

The absorption does not vary significantly across the specified application sites. Mean exposure (AUC) at each of the application sites is within approximately +/- 11% of the mean exposure for the four sites; upper outer arm, upper chest, upper back and the side of the chest.

Accidental oral ingestion: Measurable systemic levels of buprenorphine were demonstrated in dogs given NORSPAN® patch 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.

Biotransformation 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 two primary metabolites, norbuprenorphine and buprenorphine 3-O-glucuronide.

Norbuprenorphine is also glucuronidated prior to elimination. Buprenorphine is also 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 concentration at least 50-fold those seen following application of NORSPAN® patch 20 micrograms per hour.

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

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® patch repeatedly to the same site, immediate reapplication caused increased absorption, without clinical adverse events. For this reason, rotation of application sites is recommended (see Section 4.2 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 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 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.

5.3 Preclinical safety data

Systemic toxicity and dermal toxicity

In single- and repeat-dose toxicity studies in rats, rabbits, guinea pigs, dogs, and minipigs, NORSPAN® caused minimal or no adverse systemic events, whereas skin irritation was observed in all species examined. Toxicological data available did not indicate a sensitising potential of the additives of the transdermal patches

Genotoxicity and carcinogenicity

A standard battery of genotoxicity texts indicated that buprenorphine is non-genotoxic. In long-term studies in rats and mice there was no evidence of any carcinogenic potential relevant for humans.

Reproductive and developmental toxicity

No effect on fertility or general reproductive performance was observed in rats treated with buprenorphine. No embryofetal toxicity effects were observed in rats or rabbits. In a rat pre- and post-natal development toxicity study with buprenorphine there was pup mortality and decreased pup body weight at maternal doses that produced a reduction in food consumption and clinical signs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inert ingredients

Levulinic acid

Oleyl oleate

Povidone (PVP)

Duro Tak 387-2051

Duro Tak 387-2054

Polyethylene terephthalate (PET)

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

NORSPAN® patch is supplied a heat-sealed aluminium/anionic methacrylate laminate pouch. Each carton contains two individually packaged patches.

6.6 Special precautions for disposal

Disposal after use:

When changing the transdermal system, remove the used NORSPAN®, fold it over on itself (bringing the adhesive sides together) and dispose of safely, out of the reach of children.

7 MEDICINE SCHEDULE

Controlled Drug C4

8 SPONSOR

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

9 DATE OF FIRST APPROVAL

16 November 2006

10 DATE OF REVISION OF THE TEXT

06 November 2020

[CCDS V13, 19 October 2020. Orbis NZR-0066-003]

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Section 4.2	Addition of 'hot water bottles' in the list of direct external heat sources . Revision of a statement about titration of the dose every 3 days to add clarity and avoid misinterpretation.

Section 4.2, 4.3 , 4.4 and 4.8	Addition of Safety update in section 4.2, 4.3, 4.4 and 4.8 concerning 'Buprenorphine and Skin reactions'.
Section 4.4 and 4.5	Addition of warnings and precautions about Serotonin syndrome.
Section 4.5	Remove mention of oral dose buprenorphine and addition of statement of caution regarding CYP3A4.