QUALITATIVE AND QUANTITATIVE COMPOSITION

**BUPRENORPHINE (NORSPAN®)** transdermal patch is available in three strengths:

- **BUPRENORPHINE (NORSPAN®) 5 mg** contains 5 mg buprenorphine in a drug-containing matrix that releases a nominal 5 micrograms of buprenorphine per hour over 7 days.
- **BUPRENORPHINE (NORSPAN®) 10 mg** contains 10 mg buprenorphine in a drug-containing matrix that releases a nominal 10 micrograms of buprenorphine per hour over 7 days.
- **BUPRENORPHINE (NORSPAN®) 20 mg** contains 20 mg buprenorphine in a drug-containing matrix that releases a nominal 20 micrograms of buprenorphine per hour over 7 days.

PHARMACEUTICAL FORM

**BUPRENORPHINE (NORSPAN®)** is a rectangular or square, transdermal patch consisting of a protective liner and functional layers including a buprenorphine-containing adhesive matrix.

CLINICAL PARTICULARS

Therapeutic indications
For the management of moderate to severe pain.

Posology and method of administration

**BUPRENORPHINE (NORSPAN®)** should be applied to non-irritated, intact skin of the upper outer arm, upper chest, upper back or the side of the chest. **BUPRENORPHINE (NORSPAN®)** should be applied to a relatively hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped with scissors, not shaved.

Application sites should be rotated whenever a patch is replaced or added. Application sites should be reused at no less than 3-week intervals.

If the application site must be cleaned, it should be done with clear water only. Soaps, alcohol, oils, lotions, or abrasive devices should not be used. The skin must be dry before the transdermal patch is applied.

**BUPRENORPHINE (NORSPAN®)** should be worn continuously for 7 days. **BUPRENORPHINE (NORSPAN®)** should be pressed firmly in place at the application site, making sure contact is complete, especially around the edges. If the edges of the patch begin to peel off, the edges may be taped down with suitable skin tape. If a transdermal patch falls off, a new one should be applied. Bathing, showering, or swimming should not affect the patch. While wearing **BUPRENORPHINE (NORSPAN®)**, patients should be advised to avoid exposing the **BUPRENORPHINE (NORSPAN®)** site to direct external heat sources such as heating pads, electric blankets, heat lamps, etc., as an increase in absorption of buprenorphine may occur. The effects of the use of **BUPRENORPHINE (NORSPAN®)** while in hot tubs and saunas have not been studied.

Dosage and Titration:
The lowest **BUPRENORPHINE (NORSPAN®)** 5 mg should be used as the initial dose in all patients.

During initiation, titration, and treatment with **BUPRENORPHINE (NORSPAN®)**, patients may continue their existing NSAID or acetaminophen regimen as needed.

The dose of **BUPRENORPHINE (NORSPAN®)** should not be increased at less than 3-day intervals when steady-state levels are attained. Changes in **BUPRENORPHINE (NORSPAN®)** dosage may be individually titrated based on the need for supplemental PRN analgesia and the patient's analgesic response to **BUPRENORPHINE (NORSPAN®)**.

To increase the dose, a larger patch should replace the patch that is currently being worn, or a combination of patches should be applied in different places to achieve the desired dose. It is recommended that no more than two patches be applied at the same time, regardless of patch strength.

Titration should continue every 3-7 days until adequate analgesia is achieved.

If adequate pain control cannot be achieved with **BUPRENORPHINE (NORSPAN®)**, therapy should be discontinued and the patient converted to an appropriate analgesic regimen as determined by a physician.
Discontinuation:
After removal of BUPRENORPHINE (NORSPAN®), plasma concentrations decrease gradually. This should be considered when therapy with BUPRENORPHINE (NORSPAN®) is to be followed by other opioids. As a general rule, a subsequent opioid should not be administered within 24 hours after removal of BUPRENORPHINE (NORSPAN®).

Children:
The safety and efficacy of BUPRENORPHINE (NORSPAN®) in patients under 18 years of age has not been established.

Renal impairment:
No special dose adjustment of buprenorphine is necessary in patients with renal impairment.

Hepatic impairment:
There is no need for dosage adjustment when using BUPRENORPHINE (NORSPAN®) in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment may accumulate buprenorphine during BUPRENORPHINE (NORSPAN®) treatment. Consideration of alternate therapy should be given, and BUPRENORPHINE (NORSPAN®) should be used with caution, if at all, in such patients.

Elderly:
No dosage adjustment of BUPRENORPHINE (NORSPAN®) is required in elderly patients.

Conversion from opioids:
BUPRENORPHINE (NORSPAN®) can be used as an alternative to treatment with other opioids. Such patients should be started on the lowest available dose (BUPRENORPHINE (NORSPAN®) 5 mg) and continue taking short-acting supplemental analgesics (see Interactions with other medicaments) during titration, as required.

Patch application:
Applying the patch

Step 1:
Each patch is sealed in a pouch. Just before use, open the pouch by tearing where indicated. Take out the patch.

Step 2:
The sticky side of the patch is covered with a silvery protective foil. Carefully peel off half the foil. Try not to touch the sticky part of the patch.

Step 3:
Stick the patch onto the area of skin you have chosen and remove the remaining foil.

Step 4:
Press the patch against your skin with the palm of your hand and count slowly to 30. Make sure that the whole patch is in contact with your skin, especially at the edges.

Step 5:
Find a calendar that will help you remember to change your patch every 7th day. Mark the day when you put your first patch on and make a note of the time of day.

Wearing the patch
BUPRENORPHINE (NORSPAN®) should be applied to non-irritated, intact skin of the upper outer arm, upper chest, upper back or the side of the chest. Application sites should be re-used at no less than 3-week (21 days) intervals.
If a transdermal patch falls off before it needs changing, a new patch should be applied. (see “Changing the patch”).

**Changing the patch**
- Take the old patch off.
- Fold it in half with the sticky side inwards. Put the used patch into its original pouch. Now put the pouch in the bin you use for your household rubbish. Even used patches contain some active medicine that may harm children or animals, so make sure your used patches are always kept well away from them. Throw it away carefully, *out of the reach and sight of children.*
- Stick a new patch on a different appropriate skin site (as described above). You should not apply a new patch to the same site for the following 3-4 weeks.
- Mark the day and time of application on the calendar.
- Remember to change your patch at the same time of day each time.

**Contraindications**

**BUPRENORPHINE (NORSPAN®)** is contraindicated in patients with known hypersensitivity to buprenorphine or to any of the excipients (see List of excipients).

**Special warnings and precautions for use**

**BUPRENORPHINE (NORSPAN®)** should be used with caution in patients with severely impaired respiratory function and in patients concurrently receiving monoamine oxidase inhibitors (MAOIs) or who have received MAOIs within the previous two weeks.

**BUPRENORPHINE (NORSPAN®)** should be used with particular caution in patients with head injury, intracranial lesions or increased intracranial pressure, shock, a reduced level of consciousness of uncertain origin, or in patients with severe hepatic impairment (see Posology and method of administration).

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

Severe febrile illness may increase the rate of buprenorphine absorption from **BUPRENORPHINE (NORSPAN®)**.

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. (see Overdose). Caution should be exercised when prescribing **BUPRENORPHINE (NORSPAN®)** to patients known to have, or suspected of having, problems with drug or alcohol abuse or serious mental illness.

**BUPRENORPHINE (NORSPAN®)** is not recommended for analgesia in the immediate post-operative period or in other situations characterized by rapidly varying analgesic requirement.

Buprenorphine is a μ-opioid partial agonist.

Buprenorphine produces morphine-like effects, including euphoria and physical dependence, but the magnitude of these effects is less than for comparable doses of full μ-opioid agonists. 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.

**Interaction with other medicinal products and other forms of interaction**

Caution in the use of any opioid in patients taking MAOIs or who have received MAOIs within the previous two weeks is appropriate.
**BUPRENORPHINE (NORSPAN®)** should be dosed with caution in patients who are concurrently taking other CNS depressants or other drugs that may cause respiratory depression, hypotension, and profound sedation or potentially result in coma. Such agents include sedatives or hypnotics, general anesthetics, other opioid analgesics, phenothiazine, centrally acting anti-emetics, benzodiazepines and alcohol.

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

Buprenorphine is primarily metabolized 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 **BUPRENORPHINE (NORSPAN®)** with ketoconazole as compared to **BUPRENORPHINE (NORSPAN®)** alone. The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied. Co-administration of **BUPRENORPHINE (NORSPAN®)** and enzyme inducers (e.g. Phenobarbital, carbamazepine, phenytoin, and rifampin) could lead to increased clearance which might result in reduced efficacy.

**Fertility, pregnancy and lactation**

**BUPRENORPHINE (NORSPAN®)** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Buprenorphine has been shown to cross the placenta in humans. Buprenorphine has been detected in newborn blood, urine and meconium and also in mother’s milk at low concentrations. (see Preclinical safety data)

**Effects on ability to drive and use machines**

**BUPRENORPHINE (NORSPAN®)** may impair the ability to drive and operate machinery.

**Undesirable effects**

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 follow:

- Very common: ≥ 10%
- Common: ≥ 1%, < 10%
- Uncommon: ≥ 0.1%, < 1%
- Rare: ≥ 0.01%, < 0.1% (isolated cases)
- Very Rare: < 0.01%

**Immune system disorders**

- Uncommon: allergic reaction (including oropharyngeal swelling and swollen tongue
- Rare: anaphylactic responses

**Metabolism and nutrition disorders**

- Common: anorexia
- Rare: dehydration

**Psychiatric disorders**

- Common: confusion, depression, insomnia, nervousness, anxiety
- Uncommon: affect lability, agitation, euphoric mood, hallucination, decreased libido, nightmare
- Rare: psychotic disorder
- Unknown: depersonalization

**Nervous system disorders**

- Very common: dizziness, headache, somnolence
- Common: tremor
- Uncommon: concentration impairment, abnormal coordination, dysarthria, dysgeusia, hypoesthesia, memory impairment, migraine, syncope, paresthesia
- Unknown: convulsions

**Eye disorders**

- Uncommon: dry eye, blurred vision
- Rare: miosis
Ear and labyrinth disorders
Uncommon: tinnitus, vertigo

Cardiac disorders
Uncommon: palpitations, tachycardia
Rare: angina pectoris

Vascular disorders
Uncommon: flushing, hypertension, hypotension
Rare: vasodilatation, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Common: dyspnea
Uncommon: cough, hiccups, wheezing
Rare: respiratory failure, respiratory depression, aggravated asthma, hyperventilation, rhinitis

Gastrointestinal disorders
Very common: constipation, nausea, vomiting
Common: abdominal pain, diarrhea, dyspepsia, dry mouth
Uncommon: flatulence
Rare: dysphagia, ileus
Unknown: diverticulitis

Hepatobiliary disorders
Unknown: biliary colic

Skin and subcutaneous tissue disorders
Very common: pruritus
Common: rash, sweating
Uncommon: dry skin, urticaria, dermatitis contact
Rare: face edema

Musculoskeletal and connective tissue disorders
Uncommon: muscle spasm, myalgia

Renal and urinary disorders
Uncommon: urinary incontinence, urinary retention, urinary hesitation

Reproductive system and breast disorders
Rare: sexual dysfunction

General disorders and administration site conditions
Very common: application site reaction (application site erythema, application site edema, application site pruritus, application site rash)
Common: asthenic conditions (including muscle weakness), peripheral edema
Uncommon: edema, pyrexia, rigors, withdrawal syndrome, application site dermatitis**, chest pain
Rare: influenza like illness

Investigations
Uncommon: alanine aminotransferase increased, weight decreased

Injury, poisoning and procedural complications
Uncommon: accidental injury (including fall)

**In some cases late onset local allergic reactions occurred with marked signs of inflammation. In such cases treatment with BUPRENORPHINE (NORSPAN®) should be terminated.

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 apnea, 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-opioid agonists. Treatment with continuous intravenous naloxone should begin with the usual doses but high doses may be required.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Buprenorphine is a μ-opioid partial agonist. It also has antagonistic activity at the kappa-opioid receptor. It is classified as a psychotropic substance under international convention.

In a positive controlled study of effects of BUPRENORPHINE (NORSPAN®) on the QT interval in normal volunteers, 40 ug/hr was associated with a mean prolongation of the QTc interval of 5.9 msec compared to placebo. Ten mcg per hour was not different than placebo.

Endocrine system
Opioids may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

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

Like other opioid analgesics, buprenorphine has a potential risk of respiratory depression. However, evidence suggests that buprenorphine is a partial agonist with respect to its respiratory depressant activity and a ceiling effect has been reported following intravenous doses of greater than 2 μg/kg. Respiratory depression appears to be a rare occurrence at therapeutic doses of the transdermal preparation [up to 40 μg/h].

Pharmacokinetic properties
Each patch provides a steady delivery of buprenorphine for up to 7 days. Steady state is achieved during the first application. After removal of BUPRENORPHINE (NORSPAN®), buprenorphine concentrations decline, decreasing approximately 50% in 12 hours (range 10-24h).

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.

Following BUPRENORPHINE (NORSPAN®) application, buprenorphine diffuses from the patch through the skin.

Buprenorphine is approximately 96% bound to plasma proteins.

Buprenorphine metabolism in the skin following BUPRENORPHINE (NORSPAN®) application is negligible.

Norbuprenorphine is the only known active metabolite of buprenorphine.

Preclinical safety data
In single and repeat-dose toxicity studies in rats, rabbits, guinea pigs, dogs and minipigs, BUPRENORPHINE (NORSPAN®) caused minimal or no adverse systemic events, whereas skin irritation was observed in all species examined. No teratogenic effects were observed in rats or rabbits. However, perinatal mortality was reported in the literature for rats treated with buprenorphine.

A standard battery of genotoxicity tests 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.

The toxicological data available did not indicate a sensitising potential of the additives of transdermal patches.

PHARMACEUTICAL PARTICULARS
List of excipients
levulinic acid
oleyl oleate
povidone (PVP)
polyacrylate (dry solids)
polyethylene terephthalate (PET)

Incompatibilities
None known.

Shelf life
24 months

STORAGE CONDITION
Store at temperatures not exceeding 25°C.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without a prescription.
Dangerous Drugs - to be prescribed by a PDEA S-2 licensed practitioner in a DOH (yellow) prescription form.
It is a Habit-Forming Drug.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
FOR EXTERNAL USE ONLY

DOSAGE FORMS AND PACKAGING AVAILABLE
- BUPRENORPHINE (NORSPAN®) 5mg transdermal patch, box of 2’s (DR-XY35292)
- BUPRENORPHINE (NORSPAN®) 10mg transdermal patch, box of 2’s (DR-XY35290)
- BUPRENORPHINE (NORSPAN®) 20mg transdermal patch, box of 2’s (DR-XY35291)

Manufactured for: Mundipharma Distribution GmbH (Philippine Branch)
by Lohmann Therapie-Systeme AG
Unit 1706 -1709 Robinsons Equitable Tower Lohmannstrasse-2
# 4 ADB Avenue corner Poveda Street D-56626 Andernach, Germany
Ortigas Center, Pasig City
Philippines

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