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 semi-synthetic 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 a NORSpan® patch, buprenorphine concentrations decline, decreasing approximately 50% in 12 hours (range 10–24 h).

NORSpan® patches 5 micrograms/h, 10 micrograms/h and 20 micrograms/h 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/h releases 5 micrograms of buprenorphine per hour, and contains a total of 5 mg of buprenorphine. Each NORSpan® patch 10 micrograms/h releases 10 micrograms of buprenorphine per hour and contains a total of 10 mg of buprenorphine. Each NORSpan® patch 20 micrograms/h releases 20 micrograms of buprenorphine per hour and contains a total of 20 mg 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/h 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 430 L, which is indicative of the high lipophilicity of the drug.

Following IV administration, buprenorphine and its metabolites are secreted into bile, and within several minutes distribute into the cerebrospinal fluid (CSF). CSF concentrations appear to be approximately 15% to 25% of concurrent plasma concentrations.

**Metabolism and Elimination:**

Buprenorphine metabolism in the skin following 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 fæces within 7 days.

In a study in postoperative patients the total clearance of buprenorphine was 55 L/h. Norbuprenorphine is the only known active metabolite of buprenorphine. It has been shown to be a respiratory depressant in rats at concentrations at least 50-fold those seen following application of NORSpan® patch 20 micrograms/h.

Specific inhibitors of CYP450 (e.g. ketoconazole, gestodene, nifiedipine, norfluroxetin, 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 reaplication 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...
analgesia. A single trial examined the safety of three doses of NORSPAN® patches given from the skin depot. 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.

BP98-1201 was a randomised, double-blind trial comparing the efficacy and safety of NORSPAN® patches 5, 10 and 20 mg applied every 7 days with sublingual buprenorphine tablets 200 and 400 microgram [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.

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].

<table>
<thead>
<tr>
<th>Transdermal buprenorphine patches</th>
<th>Sublingual buprenorphine tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td></td>
</tr>
<tr>
<td>Titration to optimum pain control over 21 days with same dose continued for up to 28 days</td>
<td>200 or 400mcg 6–8-hourly</td>
</tr>
<tr>
<td><strong>Mean baseline pain intensity</strong></td>
<td></td>
</tr>
<tr>
<td>6.1</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Mean pain intensity scores during assessment [Day 7]</strong></td>
<td></td>
</tr>
<tr>
<td>3.2</td>
<td>3.2</td>
</tr>
</tbody>
</table>

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.

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 hydrocodeine/paracetamol).

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 hydrocodeine/paracetamol).

CONTRAINDICATIONS
NORSPAN® patches are contraindicated in patients with known hypersensitivity to buprenorphine or any components of the patch, myasthenia gravis, delirium tremens and pregnancy. NORSPAN® patches are contraindicated in patients with severely impaired respiratory function and in patients concurrently receiving non-selective monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with non-selective MAOIs. NORSPAN® patches must not be used for the treatment of opioid dependence and narcotic withdrawal.

PRECAUTIONS
NORSPAN® patches should be used with caution in patients with convulsive disorders, head injury, shock; a reduced level of consciousness of uncertain origin, intracranial lesions or increased intracranial pressure, 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 debilitating patients. As with all opioid preparations, patients who are to undergo coronary 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 overdose 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 (10 micrograms/h) had no effect on the QTc interval. Higher dosages (40 micrograms/h) and the active control (moxifloxacin 400 mg) each produced increases of 5.9 ms 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 agonists. In man limited euphoriantic 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 antagonistic properties, NORSPAN® patches may not substitute for other opioid agonists and may induce withdrawal symptoms in these patients.

Opiod Naive Patients

The lowest dose available, NORSPAN® patch 5 micrograms/h, should be used as the starting dose in opioid naive patients.

Renal Impairment

No dose adjustment is necessary in patients with renal impairment.
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 they are not safe 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 nor for at least 24 hours after the patch has been removed.

Carcinogenesis and genotoxicity:
The carcinogenic potential of buprenorphine is currently unknown. No carcinogenicity studies of NORSPAN® patch have been conducted. No evidence for carcinogenicity due to buprenorphine was noted in life time studies in mice at PO doses up to 100 mg/kg/day. In rats, however, an increased incidence of testicular tumours was observed at doses greater than 5.5 mg/kg/day. The no-effect level in both studies is at least 80 times greater than the expected daily systemic dose of buprenorphine in humans during treatment with NORSPAN® patch 20 mg, on a surface area basis. Buprenorphine showed no evidence of genotoxic activity in assays for genes mutation (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 80 mg/kg/day or daily SC doses up to 5 mg/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 20 mg, 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 drugs. 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 of 2 mg/kg/day and post-implantation losses at IV doses ≥ 0.2 mg/kg/day (drug exposure in animals about 6 times the expected daily systemic dose of buprenorphine in humans during treatment with NORSPAN® patch 20 mg, on a surface area basis). Dystocia was noted in pregnant rats treated IM with buprenorphine doses > 2 mg/kg/day (approximately the expected human daily dose during treatment with NORSPAN® patch 20 mg). Fertility and peri-partum development studies with buprenorphine in rats showed increases in neonatal mortality after doses of 0.8 mg/kg/day PO, 0.5 mg/kg/day IM or 0.1 mg/kg/day SC (approximately 14, 9 and 1.7 times, respectively; the human daily dose during treatment with NORSPAN® patch 20 mg 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 ≥ 8 mg/kg/day PO (> 100 times the expected human daily dose during treatment with NORSPAN® patch 20 mg 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 20 mg, 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 approximately 30 to 6 times, respectively; the expected human daily dose during treatment with NORSPAN® patch 20 mg, 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 postnatal 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.

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

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. Buprenorphine is metabolised to norbuprenorphine by CYP340 A4. Caution is advised when NORSPAN® patches are administered concurrently with inhibitors of CYP34A (e.g. protease inhibitors, some drug classes of azole antifungics, calcium channel antagonists and macrolide antibiotics) as this may lead to increased levels of buprenorphine. The interaction between buprenorphine and CYP34A 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. The potential exists for international normalised ratio (INR) elevation in patients who are concomitantly taking warfarin.

ADVERSE REACTIONS
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.

**Gastrointestinal**

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>constipation*, dry mouth, nausea*, vomiting*</td>
<td>anorexia, diarrhoea*, dyspepsia*</td>
<td>flatulence</td>
<td>biliary colic*, diverticulitis*, dysphagia, ileus, pyrosis (heartburn)</td>
</tr>
<tr>
<td>Nausea, retching</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Central Nervous System**

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness, somnolence*</td>
<td>anxiety, confusion, depression*, insomnia, nervousness, paraesthesia</td>
<td>affect lability, agitation, concentration impairment, coordination abnormal, depersonalization, dysarthria, dysgeusia, euphoric mood, hallucination, hypoesthesia, libido decreased, memory impairment, migraine, nightmare, restlessness, sedation, sleep disorder, syncope*, tremor</td>
<td>dysequilibrium, numbness, psychotic disorder</td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Respiratory**

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress, respiratory failure*</td>
<td>dryness*, cough, hiccups, hyperventilation, hypoxia, rhinitis*, wheezing*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cardiovascular**

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilation</td>
<td>angina pectoris, circulatory disorders (such as hypertension or rarely even circulatory collapse), flushing, hypertension*, orthostatic hypotension, palpitations, tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Genitourinary**

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence, urinary retention</td>
<td>decreased erection, sexual dysfunction, urinary hesitancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Metabolic and Nutritional**

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
<td></td>
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</table>

**Skin and Appendages**

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site reaction, pruritus*</td>
<td>erythema at site, exanthema, rash, rash at site, sweating*</td>
<td>dry skin, face oedema, urticaria</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Special Senses**

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste perversion</td>
<td>dry eye, vision blurred, miosis, vertigo</td>
<td>eye oedema, miosis, visual disturbance</td>
<td>car pain</td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
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<td></td>
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</table>

**Body as a Whole**

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache*</td>
<td>abdominal pain*, asthenia* (including muscle weakness), chest pain*, oedema, pain, peripheral oedema, tiredness</td>
<td>accidental injury (including fall), allergic reaction (including oropharyngeal swelling and swollen tongue), influenza-like illness, malaise, muscle cramp, muscle spasms, myalgia, pyrexia*, rigurs*, withdrawal syndromes</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Use In Children**

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

**Hepatic Impairment**

Buprenorphine is metabolized 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.

**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 they are not safe 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 nor for at least 24 hours after the patch has been removed.

**Use In Elderly**

The safety and efficacy of NORSPAN® patches has been established.

**Use In Pregnancy**

NORSPAN® patches in rats and rabbits (systemic exposure to buprenorphine up to about 100 times the expected human daily dose during treatment with NORSPAN® patch 20 mg, 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 approximately 30 to 6 times, respectively; the expected human daily dose during treatment with NORSPAN® patch 20 mg, 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 postnatal 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.

**Drug/Laboratory Test Interactions**

Increased aminotransferase levels and weight decrease have been noted.

**Drug Interaction**

MAOIs within the previous 14 days. As it is unknown whether there is an interaction this drug combination.
opioid tolerance, if any, as well as current general condition and medical status of the patients. Efficacy with NORSPAN® patch is attained. As a general rule, a subsequent opioid should not be administered within 24 hours of needs to be considered when use of NORSPAN® patch is to be followed by other opioids. The lowest dose, NORSPAN® patch 5 micrograms/h, should be used as the initial dose. Adults: The lowest dose, NORSPAN® patch 5 micrograms/h, should be used as the initial dose. Changes in NORSPAN® patch dosage may be individually titrated based on the need for supplemental PNR 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/h) 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 Drugs: NORSPAN® patches have been used as an alternative in patients taking lower doses of opioids (up to 90 mg of oral morphine-equivalents a day) and combination analgesics. Such patients should be started on a low dose of NORSPAN® patch and continue with the same dose and dosing schedule 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. When 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 have 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.

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. 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 narcotic antagonist, such as naloxone, may reverse the effects of buprenorphine. The dose of naloxone should begin with the usual dosages but may be in the range of 5 to 12 mg intravenously. The onset of naloxone effect may be delayed by 30 minutes or more. Maintenance of adequate ventilation is more important than treatment with naloxone.

STORAGE

Store below 25°C.

PRESENTATION

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/h
- NORSPAN® patch 10 Each patch releases buprenorphine 10 micrograms/h
- NORSPAN® patch 20 Each patch releases buprenorphine 20 micrograms/h

The area containing the active substance: 0.25 cm² Total buprenorphine content: 5 mg
The area containing the active substance: 1.25 cm² Total buprenorphine content: 10 mg
The area containing the active substance: 2.5 cm² Total buprenorphine content: 20 mg

NORSPAN® patch is supplied in cartons containing 2 individually packaged patches.

POISON SCHEDULE

S8

SPONSOR

Mundipharma Pty Limited
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SYDNEY NSW 2000

TGA APPROVAL DATE

4 April 2005

DATE OF THIS AMENDMENT

20 May 2005 (Safety-related change)
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