

# Buprenorphine transdermal patches (Norspan) for chronic severe pain

(bu-pre-NOR-fun)

## Summary

- Transdermal buprenorphine could be considered in chronic severe pain when lower doses of strong opioids are indicated. However, more familiar opioids such as morphine are preferred and offer a broader range of doses and formulations.
- Buprenorphine produces typical opioid adverse effects (constipation, headache, nausea, vomiting, dizziness).
- Avoid prescribing buprenorphine to people who may be dependent on other opioids because it can precipitate withdrawal symptoms, including pain.

## PBS listing

### Restricted benefit

Chronic, severe disabling pain not responding to non-opioid analgesics.

Authorities for increased maximum quantities will be available for patients meeting the criteria listed in the note in the *Schedule of Pharmaceutical Benefits*. See *NPS RADAR 'In Brief'*, August 2005, for details.

Buprenorphine is a schedule 8 substance and so must be prescribed in accordance with State or Territory regulations (see [www.tga.gov.au/ndpsc/stdpu.htm](http://www.tga.gov.au/ndpsc/stdpu.htm)).

### Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee recommended listing on the basis of similar safety, efficacy and cost to those for oxycodone hydrochloride controlled-release tablets (i.e. cost minimisation).<sup>1</sup> Buprenorphine transdermal patch and oxycodone controlled-release tablets have not been directly compared in clinical trials, so the economic analysis was based on an indirect comparison using immediate-release oxycodone plus paracetamol combination tablets and placebo as common comparators. For the purposes of the cost-minimisation analysis, the equi-effective doses were transdermal buprenorphine 5 mg (releasing buprenorphine 5 micrograms per hour), 10 mg (10 micrograms per hour) and 20 mg (20 micrograms per hour) every 7 days equivalent to oxycodone controlled release 10 mg, 20 mg and 30 mg twice daily, respectively.

## Place in therapy

Transdermal buprenorphine may be used in chronic severe pain when lower doses of strong opioids are indicated. However, the place of transdermal buprenorphine in pain management is not well established. More familiar and better-studied opioids such as morphine are preferred and provide a broader range of doses and formulations. The 7-day patch formulation may have a particular role for patients who are vomiting or have swallowing difficulties. The patches are the only transdermal opioid preparation listed on the PBS for non-malignant pain.

Transdermal buprenorphine patches deliver buprenorphine at a constant rate over 7 days. The dose equivalence of transdermal buprenorphine and oral morphine is not established. The manufacturer suggests that the dose range covered by the three patch strengths may be equivalent to oral morphine up to 90 mg/day.<sup>2</sup> Other literature and the dose relativities suggested for the higher-strength patches available overseas indicate that the buprenorphine 20-microgram-per-hour patch might be equivalent to oral morphine up to 36 mg/day or 53 mg/day<sup>3</sup>; however, published evidence for equi-analgesic doses is sparse and of low quality so it cannot be regarded as definitive.

There is little information available about the efficacy and tolerability of buprenorphine patches in comparison with other strong opioids because none of the studies assessing the efficacy and safety of the patches available in Australia has been published. Results of trials using the higher-strength buprenorphine patches available

overseas cannot be reliably extrapolated to the patches available in Australia. The manufacturer's submission for PBS listing mentions several trials comparing transdermal buprenorphine with either oxycodone plus paracetamol combination tablets, buprenorphine sublingual tablets or hydrocodone plus paracetamol combination tablets in people with osteoarthritis or chronic back pain.\* These studies found no significant differences in analgesic efficacy between buprenorphine and the comparators.<sup>4</sup>

Transdermal buprenorphine is not suitable for the management of acute pain because it has a slow onset and extended duration of action.

### Buprenorphine: a partial agonist

Buprenorphine is a partial agonist so there is a ceiling dose to its analgesic effect — that is, above a certain dose there is no further analgesic effect. The dose at which this occurs in humans is not established but it is unlikely at the doses in the transdermal patches.

Because of its partial agonist activity, buprenorphine may trigger opioid withdrawal symptoms in people who have developed physical dependence on other opioids.

Buprenorphine has high affinity for *mu* opioid receptors and is not easily displaced by opioid antagonists. Consequently, the effects of buprenorphine in overdose are only partially reversed by naloxone.

### Include non-drug treatment in managing pain

Pain management should involve a range of treatment modalities with an emphasis on non-drug treatment. Non-drug treatments may include those directed at improving physical function (such as exercise and physiotherapy), psychological wellbeing (such as cognitive behavioural therapy and stress management) and encouraging return to normal activity.<sup>5–7</sup>

Ensure that patients understand the goals of treatment and have realistic expectations. It is usually not possible to eliminate pain completely. In chronic non-cancer pain, the goal of treatment is to maintain or restore function and improve quality of life as well as to provide pain relief.<sup>5</sup> In cancer pain, providing pain relief is the primary goal.

\*Doses were oxycodone with paracetamol 5 mg/325 mg 1–3 tablets 4 times daily, buprenorphine sublingual tablets 200 micrograms or 400 micrograms 6–8-hourly and hydrocodone with paracetamol 2.5 mg/250 mg 1–3 tablets 4 times daily.

A written pain-management plan helps to ensure that all members of the healthcare team take a consistent approach to the patient's pain management and helps patients take an active role in managing their own pain.<sup>6</sup>

### Chronic non-cancer pain: consider an opioid when other analgesics are inadequate

A stepwise approach is appropriate, starting with non-opioids. Paracetamol is the drug of choice in mild to moderate pain. Add or substitute a nonsteroidal anti-inflammatory drug if paracetamol is inadequate. Consider adding or substituting a weak opioid (codeine or tramadol) if the patient does not respond to non-opioids.<sup>6</sup> Encourage regular (rather than as-needed) use of analgesics and titrate to maximum doses before moving to the next step.<sup>6</sup>

Strong opioids (such as morphine, oxycodone and buprenorphine) should only be considered for patients who do not respond to other treatments. Before opioids are prescribed, the potential benefits should be weighed against the possibility of adverse effects and misuse. Consider whether the patient should be assessed by a specialist pain team before opioids are started.

Published clinical trial evidence for opioids in chronic non-cancer pain is scarce, so guidelines for opioid prescribing rely largely on clinical experience and consensus.

For more information, see the NSW Therapeutic Advisory Group's *General principles: rational use of opioids in chronic or recurrent non-malignant pain*.<sup>6</sup>

### Cancer pain: buprenorphine patches less suitable

The transdermal buprenorphine patch available in Australia has not been evaluated in cancer pain. Other opioids are more suitable in cancer pain because there is extensive experience with them and they provide a greater choice of dose forms and larger dose range to control severe cancer pain.

## Safety issues

Buprenorphine produces typical opioid adverse effects (such as constipation, headache, nausea, vomiting, dizziness). Local irritation may occur at the application site.

Buprenorphine has a long half-life, so plasma concentrations fall slowly after the patch is removed. Another opioid should not be started within 24 hours of removing a patch.<sup>8</sup>

## Dependence and abuse potential

Physical dependence may develop with chronic use of buprenorphine. If a withdrawal syndrome does occur when buprenorphine is discontinued, it is usually of mild to moderate intensity, occurs within 2 days and resolves within 2 weeks.<sup>8,9</sup>

Avoid prescribing buprenorphine to people who may be dependent on other opioids because it can precipitate withdrawal symptoms, including pain. The severity of the withdrawal syndrome will depend on the degree of physical dependence and the dose of buprenorphine given.<sup>8</sup>

Transdermal buprenorphine may have lower abuse potential than other buprenorphine dosage forms because of the relatively low plasma concentrations achieved, the slow onset of effect and because it is likely to be difficult to extract the drug from the matrix design. Misuse could take the form of using excessive amounts of the intact patch or applying it to sites that would enhance systemic absorption. It should be used with caution in people with a past history of dependence on alcohol or other drugs.

## Overdose: effects only partially reversed by naloxone

In overdose the effects of buprenorphine are only partially reversed by naloxone.<sup>9</sup> The manufacturer states that the dose of naloxone should start in the usual range but that naloxone 5–12 mg intravenously may be required.<sup>8</sup> Repeated naloxone doses may be needed because naloxone has a shorter duration of action than buprenorphine. Management of overdose should focus on maintaining adequate ventilation.<sup>9</sup>

There is likely to be a lower risk of overdose with buprenorphine patches than with other dose forms (sublingual tablets and injection) because the doses administered via the patches are much lower.

The respiratory depressant effects of buprenorphine are subject to a ceiling effect. However, significant respiratory depression has been reported with buprenorphine, particularly when it is administered intravenously. Deaths have been associated with very high doses or inappropriate use of buprenorphine (such as crushing and injecting sublingual tablets) in combination with benzodiazepines or other central nervous system depressants.<sup>9</sup>

## Dosing issues

Buprenorphine patches are available in three strengths: 5 micrograms per hour, 10 micrograms per hour and 20 micrograms per hour.

Opioid-naïve patients should start at the lowest strength. Supplemental analgesics should be continued as needed during titration because buprenorphine concentrations rise slowly. Patients converting from other opioids (up to the equivalent of oral morphine 90 mg/day) can also begin on a low strength of buprenorphine and should continue with their previous regimen during titration.<sup>8</sup>

Use non-opioid analgesics for breakthrough or incident pain.<sup>5</sup> In clinical trials, simple analgesics (such as paracetamol with or without codeine) were used when additional analgesia was required.

The dose should be titrated to effect and should not be increased at intervals of less than 3 days. To increase the dose, remove the current patch and apply a higher-strength patch or a combination of 2 patches. No more than two 20-microgram-per-hour patches should be used at once. The patches should not be cut because this may compromise the accuracy of dosing.

New patches should always be applied to a different site from the previous one. Any site should not be re-used for 3–4 weeks to minimise the risk of local skin irritation and because immediately re-using a site can increase the rate of absorption of buprenorphine.

The Norspan product information contains detailed instructions for applying patches.

## Information for patients

Ensure that patients understand how to correctly use and dispose of buprenorphine patches.

Detailed information about applying the patch is given in the Norspan consumer medicine information (CMI). An illustrated leaflet explaining patch application is available from the manufacturer, Mundipharma Pty Ltd (ph 1800 188 009).

In particular, patients should be advised:

- not to apply a new patch to the same application site for 3–4 weeks to reduce the chances of local skin irritation
- that the patch does not need to be applied to the site of the pain. It should be applied to a nearly hairless site on the upper outer arm, upper chest, side of the chest or upper back
- to avoid exposing the application site to heat (such as electric blankets, saunas, heat lamps or intensive

sunbathing) because this may increase the level of buprenorphine in their blood and increase the risk of adverse effects

- to speak to their doctor if they are using the patch during a severe fever, because this may also increase blood buprenorphine levels. Using the patch during mild fever is unlikely to affect the level of buprenorphine in their blood
- to fold used patches in half (with the sticky sides together) and dispose of them out of reach of children.

Discuss the potential adverse effects of buprenorphine. Most adverse effects reduce with time. Constipation may persist; advise patients to drink adequate amounts of water, increase their fibre intake and remain as mobile as possible. Regular laxatives (combined stool softener with stimulant laxative, such as Coloxyl with Senna, or an osmotic laxative, such as sorbitol or lactulose) should be started when buprenorphine is initiated and continued for long as buprenorphine or other opioids are used.

## References

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.