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Buprenorphine 5, 10 and 20 μg/h Transdermal Patch: A Guide to Its Use in Chronic Non-Malignant Pain

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Abstract

Buprenorphine lower-dose (5, 10 and 20 μg/h) transdermal patches, which are administered once every 7 days, are indicated in the management of chronic non-malignant pain. This review focuses on the labelling of this formulation (BuTrans®) in the EU. The analgesic efficacy of transdermal buprenorphine in patients with osteoarthritis of the hip and/or knee has been demonstrated to be equivalent to sublingual buprenorphine, noninferior to prolonged-release tramadol and generally superior to a matching transdermal placebo patch. When used together with regularly scheduled oral paracetamol (acetaminophen), transdermal buprenorphine was noninferior to codeine plus paracetamol. Transdermal buprenorphine has also shown analgesic efficacy in patients with chronic non-malignant pain of various causes.

What is the rationale for developing the drug?

Chronic non-malignant pain, such as low back pain or pain associated with osteoarthritis, is a major health problem that is often inadequately treated.[1] Various treatment guidelines are available for the pharmacological management of chronic non-malignant pain; these generally recommend a combination of opioids and non-opioids for the relief of moderate or more severe pain.[2-4] Although it is recognized that many recommendations regarding the use of opioids will be based on clinical experience and best opinion,[5] some agents may be preferred in certain patient populations.

Buprenorphine transdermal patches at the lower dose of 5, 10 and 20 μg/h (BuTrans® [EU; US]), which are administered once every 7 days, have been developed to manage chronic non-malignant pain.

How does the drug work?

The analgesic activity of buprenorphine is mediated primarily via partial agonism at the μ-opioid receptor, although buprenorphine is described to function as a pure μ-receptor agonist at typical analgesic doses.[6] The drug also has antagonistic activity at the κ-opioid receptor.[6] It binds to μ- and κ-receptors with high affinity.[7]

For whom is the drug indicated?

Buprenorphine lower-dose (5, 10 and 20 μg/h) transdermal patches are indicated in the management of chronic non-malignant pain in many countries worldwide. For simplicity, the 7-day lower-dose formulation is referred to hereafter as transdermal buprenorphine.

In the EU, transdermal buprenorphine is indicated for the treatment of adults with non-malignant

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What are the key clinical benefits and limitations of transdermal buprenorphine in chronic non-malignant pain?
Clinical benefits
Applied once weekly
Provides consistent plasma drug concentrations over the 7-day dosing interval
Potentially useful in patients who are vomiting or have swallowing difficulties
Ceiling effect for respiratory depression (main risk is when combined with other CNS depressants)
Better tolerated than sublingual buprenorphine
Limitations
Relatively slow onset of action and less flexibility in terms of dosage adjustments compared with oral or parenteral opioids
As with other opioids, persistence with therapy is difficult for many patients because of adverse events and other factors
As with other opioids, physical dependence can develop, and withdrawal symptoms do occur in some patients after discontinuation
As with other opioids, its use is contraindicated or requires caution in certain patient populations or when used concomitantly with certain drugs
In the case of overdose, the maintenance of adequate ventilation is more important in treating respiratory depression than treatment with naloxone; intravenous naloxone may reverse the effects of buprenorphine, but the onset of its effect may be delayed by ≥30 min and the effect may be incomplete

pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia.[6] It should not be used for the treatment of acute pain. A summary of the EU prescribing information for transdermal buprenorphine is provided in table I.

What is its therapeutic efficacy …

The therapeutic efficacy of transdermal buprenorphine in chronic non-malignant pain has been evaluated in randomized, controlled trials in patients with persistent non-malignant pain syndromes.[8-15] The main instruments used to assess pain in these trials are summarized in table II. For all of these instruments, lower scores indicate less pain.

… in patients with osteoarthritis …

The analgesic efficacy of transdermal buprenorphine in patients with pain of at least moderate severity associated with osteoarthritis of the hip and/or knee has been demonstrated in several trials, which have shown the formulation to be equivalent to sublingual buprenorphine,[9] noninferior to prolonged-release tramadol tablets,[10] noninferior to co-codamol (codeine plus paracetamol [acetaminophen]) combination tablets (when transdermal buprenorphine was used together with regularly scheduled oral paracetamol)[12] and generally superior to a matching transdermal placebo patch.[8,11] Across the studies, transdermal buprenorphine was associated with improvements from baseline for various primary and secondary assessments of pain or other clinical efficacy outcomes.[8-12] Active comparators and placebo also showed improvements from baseline for these endpoints, although the magnitude of improvement was generally less with placebo than with transdermal buprenorphine.[8-12]

In general, patients were required to discontinue other analgesic therapy prior to randomization;[8-12] however, in one trial, patients continued to receive their high-dose NSAID or COX-2 inhibitor.[8]

The two placebo-controlled[8,11] and three active-comparator[9,10,12] trials were of 5–26 weeks' duration, which included dosage-titration and assessment periods. In the active-comparator trials, analgesic equivalence or noninferiority was assumed if the 95% CI for the mean treatment difference for NRS-11 pain scores fell between −1.5 and 1.5 (in some cases only the lower value was specified).[9,10,12]

In a 6-month trial (n = 311), transdermal buprenorphine had a numerically greater effect than

Table I. Summary of EU prescribing information[6] for the 7-day lower-dose (5, 10 and 20 μg/h) buprenorphine transdermal patch (BuTrans®) in the treatment of adults (aged ≥18 y) with non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia[a]

How should it be administered?	
Application site	Upper outer arm, upper chest, upper back or the side of the chest
Duration	Patch(es) should be worn continuously for 7 days (unless earlier dosage titration is necessary)
Rotation of site	Rotation of the application site is recommended, such that a new patch is not applied to the same skin site for the next 3 or 4 weeks
Starting dose	5 μg/h
Dosage adjustment	Gradual upward dosage titration until adequate pain relief is achieved; dosage should not be increased before 3 days (to allow maximum effect of a given dose); no more than two patches should be applied at the same time to achieve the desired dose
Maximum dosage	40 μg/h[b]
What is its pharmacokinetic profile?	
Time to steady state	Achieved during the first application
Absorption	Affected by application site (e.g. may be markedly reduced if a non-recommended site is used) and by repeated use of the same site within too short a time frame (potentially doubling exposure to the drug)
Metabolism	Undergoes hepatic metabolism, primarily via CYP3A4 isoenzymes to norbuprenorphine (the only active metabolite, with activity ≈40-fold lower than the parent compound) and via UDP-glucuronosyltransferase isoenzymes to buprenorphine 3-O-glucuronide
Elimination	Metabolites eliminated via biliary and renal excretion
How should it be used in special populations?	
Elderly pts	No need for dosage adjustment (pharmacokinetic profile is similar between elderly and young healthy volunteers)
Pts with renal impairment	No need for dosage adjustment (pharmacokinetic profile is not affected by renal impairment)
Pts with hepatic impairment	Mild to moderate impairment: monitor pts carefully (e.g. for signs of increased CNS depression) Severe impairment: use with caution, if at all
Are there any potential drug interactions?	
Benzodiazepines	May potentiate respiratory depression of central origin, with risk of death
Other CNS depressants	May increase CNS depressant activity
CYP3A4 inhibitors	Potential for increased plasma buprenorphine concentrations and an associated increase in CNS depressant effects
CYP3A4 inducers	Potential for reduced plasma buprenorphine concentrations and an associated reduction in analgesia
MAOIs	Use of transdermal buprenorphine is contraindicated in pts who have recently (within 2 wk) received MAOI treatment
Drugs that reduce hepatic blood flow	May result in a decreased rate of hepatic elimination of buprenorphine

a Consult local prescribing information for further details. Note that there are important differences between labelling in the EU[6] and other countries.

b Although a maximum dosage is not explicitly specified, it is recommended that no more than two patches of transdermal buprenorphine are applied at the same time, regardless of patch strength, thereby implying a maximum dosage of 40 μg/h.

CYP = cytochrome P450; **MAOI** = monoamine oxidase inhibitor; **pts** = patients.

placebo in terms of the improvement from baseline in WOMAC OA index score (primary endpoint), but the between-group difference did not achieve statistical significance ($p = 0.061$).[8] There were, however, statistically significant ($p < 0.05$) advantages favouring transdermal buprenorphine for various secondary outcomes, including movement-related daytime pain on the NRS-11.[8] A 5-week trial showed a statistically significant advantage for transdermal buprenorphine over placebo for the proportion of patients who rated their pain relief as being at least 'good' (44% vs 32%; $p < 0.05$).[11]

The analgesic equivalence of transdermal buprenorphine 5–20 μg/h every 7 days and sublingual buprenorphine 600–1200 μg/day in divided daily doses was demonstrated in the per-protocol population of 102 patients with osteoarthritis in a 7-week trial.[9] Transdermal buprenorphine 5–20 μg/h every 7 days was also noninferior to orally administered prolonged-release tramadol 75–200 mg twice daily in a 12-week trial in 134 osteoarthritis patients.[10] In addition, when combined with regularly scheduled paracetamol (1 g orally four times daily), transdermal buprenorphine 5–25 μg/h had analgesic efficacy that was noninferior to that of co-codamol (codeine/paracetamol 16 mg/1 g–60 mg/1 g orally four times daily) in the per-protocol population of 117 patients in a 22-week trial.[12]

… low back pain …

Transdermal buprenorphine was significantly more effective than placebo in reducing low back pain of at least moderate severity (≥2 on a 5-point verbal categorical scale) in two 4-week, crossover trials (table III).[13,14] In one study, more than half of the patients had not previously received opioids for their low back pain,[14] whereas the other study included only opioid-experienced patients.

As shown in table III, transdermal buprenorphine was associated with significantly greater improvements in pain scores than placebo for both co-primary endpoints in both crossover studies in the per-protocol populations.[13,14] In both studies, transdermal buprenorphine and placebo were also associated with significant ($p < 0.05$) improvements from baseline for a number of secondary endpoints, with an overall trend favouring active therapy, but with few statistically significant differences between treatment groups.[13,14]

… or other types of chronic non-malignant pain?

A maintenance-of-analgesia study demonstrated the analgesic efficacy of transdermal buprenorphine in patients with chronic non-malignant pain (of various causes) that was controlled with oral opioid combination agents.[15] In the modified intent-to-treat population ($n = 266$), the proportion of patients with ineffective treatment was significantly higher with placebo than with transdermal buprenorphine (65.0% vs 51.2%; odds ratio 1.79; 95% CI 1.09, 2.95; $p = 0.022$). Observational studies also support the analgesic efficacy of transdermal buprenorphine in chronic non-malignant pain.[17,18]

Table II. Main instruments used to assess chronic non-malignant pain in randomized controlled trials of transdermal buprenorphine

Instrument	Description
NRS-11	Pain intensity on an 11-point scale where 0 = no pain and 10 = pain as bad as you can imagine
5-Point verbal categorical scale	Pain intensity on a 5-point scale as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = excruciating
VAS 100 mm	Pain intensity assessed using a 100 mm unmarked line from no pain to excruciating pain
WOMAC OA index	Pain subscale includes five items (during walking, using stairs, in bed, sitting/lying and standing) each rated on a scale from 0 (none) to 4 (extreme) [pain score range 0–20][a]

a Also available in a 100 mm VAS format, although various methods of aggregating scores have been used, so the range of possible total scores may vary.[16]

NRS = numeric rating scale; **VAS** = visual analogue scale; **WOMAC OA** = Western Ontario and McMaster Universities osteoarthritis.

Table III. Main findings of randomized, double-blind, 4 wk, crossover trials with transdermal buprenorphine in patients with low back pain of at least moderate severity

Study	Treatment[a] (no. of pts)	VAS 100 mm		5-Point verbal categorical scale	
		Baseline	Assessment phase	Baseline	Assessment phase
Gordon et al.[14] b	BUP-TD 5–20 μg/h (53)	62.1	37.6*	2.5	1.7*
	Placebo (53)	62.1	43.6	2.5	2.0
Gordon et al.[13] c	BUP-TD 10–40 μg/h[d] (52)	60.9	45.3*	2.6	1.9*
	Placebo (52)	60.9	53.1	2.6	2.2

a Dosages were titrated to response during the first 3 wk.

b More than half (58%) of pts were naive to opioids.

c All pts had previously received opioids.

d Dosages >20 μg/h were achieved by using two patches at the same time.

BUP-TD = transdermal buprenorphine; **pts** = patients; **VAS** = visual analogue scale; * $p < 0.05$ vs placebo.

What is the tolerability profile?

In general, serious adverse events with transdermal buprenorphine are similar to those for other opioid analgesics, including respiratory depression (especially when used with other CNS depressants) and hypotension.[6] However, buprenorphine demonstrated a ceiling effect for respiratory depression (but not for analgesia) when dosages were increased in healthy volunteers,[19-21] and the main risk of clinically significant respiratory depression with transdermal buprenorphine is when it is used with other CNS depressants.[6,20,21] In terms of the overall tolerability profile of transdermal buprenorphine, the most frequently reported adverse events (≥10% of patients) are headache, dizziness, somnolence, constipation, dry mouth, nausea, vomiting, pruritus, erythema, application-site pruritus and application-site reactions.[6]

In active-comparator trials, transdermal buprenorphine had a broadly similar tolerability profile to that of orally administered co-codamol[12] and prolonged-release tramadol,[10] but was better tolerated than sublingually administered buprenorphine (figure 1).[9]

In a study in healthy volunteers, transdermal buprenorphine 10 μg/hour had no clinically meaningful effect on corrected QT (QTc) intervals; however, transdermal buprenorphine 40 μg/hour prolonged the mean QTc interval by a maximum of 9.2 msec across 13 assessment timepoints during steady state (i.e. fourth day of application).[22] Although the EU summary of product characteristics[6] does not mention an increased risk of QTc interval prolongation with transdermal buprenorphine, the US prescribing information[22] states that its use should be avoided in patients with long QT Syndrome, a family history of long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications, and that these observations should be considered when prescribing

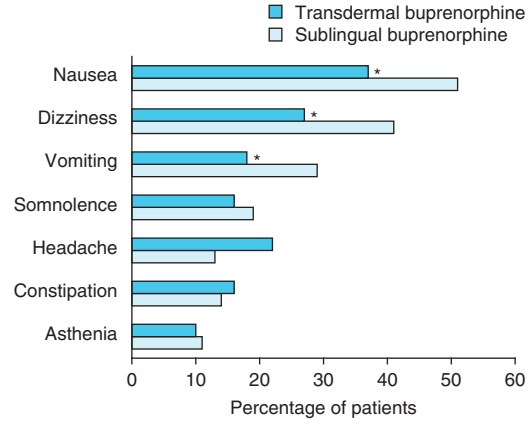

Fig. 1. Tolerability profile of transdermal vs sublingual buprenorphine in patients with moderate to severe osteoarthritis pain. Most frequently reported adverse events with transdermal buprenorphine 5–20 μg/h every 7 days (n = 118) or sublingual buprenorphine 600–1200 μg/day in divided doses (n = 120) during a 7-week, randomized, double-blind trial (3-week titration period and 4-week assessment period).[9] * $p < 0.05$ vs sublingual buprenorphine.

transdermal buprenorphine to patients with hypokalaemia or clinically unstable cardiac disease.

As with all opioids, physical dependence may develop, and withdrawal symptoms, such as agitation and anxiety, occur in some patients, usually beginning 2 days after discontinuation of transdermal buprenorphine and lasting for up to 2 weeks.[6]

What is the current positioning in this indication?

The 7-day lower-dose formulation of transdermal buprenorphine is among the options for the opioid management of moderate chronic non-malignant pain in selected patients. It has demonstrated analgesic efficacy and was generally well tolerated in clinical trials in patients with chronic non-malignant pain. This transdermal formulation of buprenorphine has the convenience of administration once per week, and may be suitable for patients with swallowing difficulties or impaired gastrointestinal function, or those who are experiencing vomiting. The use of transdermal buprenorphine should be considered only in appropriate patients, as its use is contraindicated or requires caution in certain patient populations or when used concomitantly with certain drugs. Of note, because the long time to steady state prevents rapid titration of the dose, transdermal formulations of opioids are not suitable for the treatment of acute pain or in patients whose analgesic requirements are changing rapidly.

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