CEDAC FINAL RECOMMENDATION

BUPRENORPHINE TRANSDERMAL PATCH RESUBMISSION
(BuTrans – Purdue Pharma)
Indication: Pain, Persistent (Moderate Intensity)

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that buprenorphine transdermal patch not be listed.

Reason for the Recommendation:
In the three randomized controlled trials (RCTs) included in the systematic review considered by CEDAC, buprenorphine transdermal patch did not provide statistically significantly greater reductions in pain compared with oral opioid formulations, and buprenorphine transdermal patch is more costly than many available opioid formulations.

Of Note:
The Committee noted that the frequency of gastrointestinal adverse events was similar between buprenorphine transdermal patch and the oral opioid comparators in the systematic review.

Background:
Buprenorphine transdermal patch has a Health Canada indication for the management of persistent pain of moderate intensity in adults requiring continuous opioid analgesia for an extended period of time. Buprenorphine is an opioid receptor agonist and antagonist analgesic. Three strengths of buprenorphine transdermal patch are available in Canada: 5 mg, 10 mg, and 20 mg per patch, delivering 5 mcg per hour, 10 mcg per hour, and 20 mcg per hour of buprenorphine, respectively, for seven days. Health Canada recommends that treatment be initiated at the lowest available dose (5 mcg per hour), particularly in opioid-naive patients. Opioid-experienced patients may initiate treatment at 10 mcg per hour. The maximum recommended buprenorphine transdermal patch dose is 20 mcg per hour.

Submission History:
Buprenorphine transdermal patch was previously submitted to the Common Drug Review (CDR), and discussed by CEDAC at the March 2011 meeting; however, the manufacturer elected to file a resubmission before the Notice of Final Recommendation was issued.

Thus, the original submission was stopped. The basis for this resubmission is a new confidential reduced price. The manufacturer did not submit new clinical information.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the CDR: a systematic review of RCTs of buprenorphine transdermal patch, a critique of the manufacturer's pharmacoeconomic evaluation, patient group-submitted information about outcomes and issues important to patients, and the new confidential price.

Clinical Trials
The systematic review included two double-blind RCTs of patients with back pain, and one open-label RCT of patients with moderate to severe pain related to osteoarthritis of the hip and/or knee.

- BUP3015 (N = 662) included a 12-week double-blind double-dummy RCT of three fixed-dose treatment groups: oxycodone immediate release (IR) 10 mg orally every six hours, and either buprenorphine 5 mg or 20 mg transdermal patch applied every seven days. Prior to randomization, patients were required to demonstrate response to and tolerability of buprenorphine 20 mg transdermal patch during a three-week run-in period. Included patients had a history of low back pain for three months or more and a history of oral opioid use (equivalent to 30 mg to 80 mg of morphine per day) for at least four days per week for a minimum of 30 days before study entry. Approximately 35% of patients withdrew following randomization.
- BP96-0604 (N = 134) was a 12-week double-blind double-dummy RCT that included three treatment groups: placebo, buprenorphine transdermal patch, and combination oxycodone 5 mg plus acetaminophen 325 mg oral tablets. Dosages were titrated to effect during the first three weeks of the study; allowable dosage ranges were buprenorphine transdermal patch 5 mg to 20 mg applied once every seven days, and one to three tablets of oxycodone 5 mg plus acetaminophen 325 mg four times a day. Included patients had back pain for more than two months and were receiving a stable dose of a nonsteroidal antiinflammatory drug (NSAID) for at least two weeks before study entry. *[Confidential information related to this study, including mean final doses of study medication were removed at manufacturer's request.]* Approximately 50% of patients withdrew from the trial.
- BUP4009 (N = 135) was a 12-week open-label RCT designed to test the non-inferiority of buprenorphine transdermal patch compared with tramadol controlled-release (CR) tablets. Dosages could be adjusted at any time during the trial; allowable dosage ranges included buprenorphine transdermal patch 5 mg to 20 mg applied once every seven days, and tramadol CR 75 mg to 200 mg twice daily. Included patients had moderate to severe pain related to osteoarthritis of the hip and/or knee with inadequate pain relief with acetaminophen 4 g per day over a one-week screening period. Mean doses of study medication during the trial were between 10 mg and 15 mg per week for buprenorphine and 300 mg per day for tramadol CR. Approximately 26% of patients withdrew following randomization.

The run-in period of BUP3015 preferentially selected patients who were responsive and tolerant of buprenorphine transdermal patch, likely biasing results in favour of this drug. All trials were limited by high numbers of withdrawals, which were unbalanced across treatment groups.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: pain intensity, quality of life, functional status, total withdrawal, adverse events, and withdrawal due to adverse events.

The primary outcome in all three trials was average pain, which was reported using numerical rating scales of 0 to 10, including the 11-point box scale (BS-11) where 0 = "no pain" and 10 = "worst imaginable pain". The methods used to collect data on the primary outcome varied between the trials, as described below:

- BUP3015 – average pain during the last 24 hours. Scores were collected during visits.
- BP96-0604 – average pain since last visit, collected during visits.
- BUP4009 – mean weekly BS-11 pain score, collected in subject diaries every evening for average pain during the day. The non-inferiority margin was –1.5 boxes on the BS-11 scale.

The Committee considered other outcomes noted to be of importance to patients, such as functional abilities and quality of life. Data on the former outcomes were available from the reviewed trials; however, none of the reviewed trials specifically examined patients' ability to remain at or return to work.

Results

Efficacy or Effectiveness

- Because of high and differential between-treatment study withdrawals, the Committee considered the following analyses when examining change from baseline in pain scores: the baseline observation carried forward analyses in BUP3015 and BP96-0604, and the per-protocol analysis for the non-inferiority testing in BUP4009.
- In BUP3015, both buprenorphine 20 mg and oxycodone IR exhibited statistically significantly greater reductions in average pain scores compared with buprenorphine 5 mg; mean difference (MD): –0.60 and –0.84 for buprenorphine 20 mg and oxycodone IR, respectively. Statistical testing between buprenorphine 20 mg and oxycodone IR was not conducted.
- In BP96-0604, buprenorphine exhibited a statistically significantly greater reduction in average pain score compared with placebo; MD: –0.97. *[Details regarding the comparison of oxycodone plus acetaminophen with placebo were removed at the manufacturer's request.]* The difference between the active treatments was not statistically significant.
- In BUP4009, buprenorphine was considered non-inferior to tramadol CR, as the lower bound of the 95% confidence interval (CI) of the MD for change in pain scores did not cross –1.5; MD: –0.26, 95% CI: –1.11 to 0.59.
- In BUP3015 and BP96-0604, small improvements in the Oswestry Disability scores, which were not considered clinically meaningful, were observed for all treatments.

- Few statistical comparisons were reported for quality of life measures in the trials, and the clinical relevance of the differences between active treatments is uncertain.

Harms (Safety and Tolerability)

- Withdrawal due to adverse events occurred frequently with all active treatments in all trials.
- The proportion of patients experiencing adverse events was similar between buprenorphine 20 mg and other active comparators.
- Only one case of respiratory depression was reported, experienced by a patient in BUP3015 receiving buprenorphine 5 mg.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing the price of buprenorphine transdermal patch with oxycodone CR, based on the assumption of similar efficacy and harms. No head-to-head trials comparing buprenorphine transdermal patch with oxycodone CR were available; therefore, the manufacturer relied on an indirect comparison. In the absence of dose equivalence data for buprenorphine transdermal patch, the manufacturer considered codeine CR (300 mg) to be equal to the 5 mg buprenorphine transdermal patch.

Based on recommended doses, the daily cost of buprenorphine transdermal patch (5 mcg per hour, $1.73; 10 mcg per hour, *[confidential information removed at manufacturer's request]*; 20 mcg per hour, *[confidential information removed at manufacturer's request]*) is similar to oxycodone CR (10 mg to 40 mg every 12 hours; $1.74 to $4.51); longer-acting formulations of hydromorphone ($2.02 to 4.03); fentanyl patch ($1.22 to $4.02); and tramadol CR ($1.60 to $4.00). It is more expensive compared with codeine CR, hydromorphone CR, and sustained-release morphine products.

Patient Input Information:

The following is a summary of information provided by two patient groups that responded to the CDR Call for Patient Input:

- The impact of pain on life satisfaction and the ability to perform work and daily activities are important considerations to patients. Sleep disturbances and psychological distress due to pain, and gastrointestinal adverse effects of pain medications were also noted to be of concern.
- Patient expectations for buprenorphine transdermal patch are related to its unique drug delivery method (transdermal) compared with oral medications and include reduction in peaks and valleys of pain relief, improved compliance, and reduced gastrointestinal irritation. Patients indicated that transdermal delivery may reduce abuse and misuse of opioids.

Other Discussion Points:

- The Committee considered whether there was evidence to support a listing recommendation for buprenorphine transdermal patch in patients unable to take oral medications, and/or unable to self-administer medications. However, none of the reviewed trials examined the comparative efficacy and safety of buprenorphine transdermal patch in this patient population. Similarly, none of the reviewed trials specifically enrolled patients who were unresponsive to, or intolerant of, conventional opioids.

- The Committee discussed the manufacturer's suggestion that buprenorphine transdermal patch has a potential advantage over other opioid analgesics in elderly patients because no dose adjustment is necessary in patients with renal impairment. However, the Committee noted that only a small proportion of patients in the reviewed trials were older than 75 years of age and there was no description of patients' baseline renal function. Thus, there is limited RCT evidence of the efficacy and safety of buprenorphine transdermal patch compared with other opioid formulations in this patient population.
- If respiratory depression occurs with buprenorphine it cannot be readily reversed with a narcotic antagonist, due to slow dissociation of the drug from the mu-opioid receptor.

CEDAC Members:
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. James Silvius.

July 20, 2011 Meeting

Regrets:
None

Conflicts of Interest:
None

September 21, 2011 Meeting

Regrets:
Two CEDAC members did not attend

Conflicts of Interest:
None

About this Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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