



Canadian Expert Drug Advisory Committee Final Recommendation – Plain Language Version

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

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that BuTrans, which is also called buprenorphine transdermal (skin) patch, not be listed by Canada's publicly funded drug plans for the treatment of persistent moderate pain.

Reason for the Recommendation:

BuTrans did not provide greater pain relief compared with oral opioid analgesics in the three medical studies reviewed by CEDAC. In addition, BuTrans costs more than many available opioid analgesic products.

Of Note:

The Committee noted that the amount of gastrointestinal (stomach and intestine) side effects was similar between BuTrans and the oral opioid analgesics that were used in the three studies.

Background:

BuTrans belongs to a class of drugs called opioid analgesics. BuTrans is a transdermal (transmitted through the skin) patch that slowly releases buprenorphine over a period of seven days to help control moderate, persistent pain. It is approved by Health Canada for the management of persistent pain of moderate intensity in adults requiring continuous opioid analgesia for an extended period of time.

BuTrans is a thin, adhesive, rectangular or square patch that is placed on the skin. BuTrans delivers an opioid analgesic called buprenorphine continuously through the skin and into the bloodstream to control pain around-the-clock.

Three strengths of BuTrans are available in Canada: 5 mg, 10 mg, and 20 mg per patch, delivering 5 mcg/hour, 10 mcg/hour, and 20 mcg/hour of medication, respectively, for seven days. Health Canada recommends that treatment be initiated at the lowest available dose

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(5 mcg/hour), particularly in opioid-naïve (have not taken opioids before) patients. Patients who have already used opioids previously may initiate treatment at 10 mcg/hour. The maximum recommended BuTrans dose is 20 mcg/hour.

Submission History:

BuTrans was previously submitted to the Common Drug Review (CDR), and discussed by CEDAC at the March 2011 meeting; however, the manufacturer chose to file a resubmission before the Notice of Final Recommendation was given. 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:

To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of BuTrans, and a review of economic information prepared by the manufacturer of BuTrans. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug, and the new confidential price.

Clinical Trials

The systematic review included two studies of patients with back pain, and one study of patients with moderate to severe pain from osteoarthritis of the hip and/or knee.

- BUP3015 with 662 patients included a 12-week-long study period in which patients received one of three different treatments: oxycodone immediate release (IR) 10 mg orally every six hours, or either BuTrans 5 mg or 20 mg applied every seven days. Before being given one of the study treatments, patients had to use BuTrans 20 mg for three weeks and confirm that it was working for them and that they could tolerate using it. Patients in this study had low back pain for three months or more, and had previously used oral opioid analgesics (equal to 30 mg to 80 mg of morphine per day) for at least four days per week for a minimum of 30 days before starting the study. Approximately 35% of patients stopped taking part during the study over the 12 weeks.
- BP96-0604 with 134 patients was a 12-week-long study of three treatment groups: placebo (a tablet or patch containing no active medication), BuTrans, or oxycodone 5 mg plus acetaminophen 325 mg combination oral tablets (also called Percocet). Dosages were adjusted over the first three weeks of the study. Allowable dosages of BuTrans ranged from a 5 mg to a 20 mg patch applied once every seven days, and allowable dosages of oxycodone 5 mg plus acetaminophen 325 mg tablets ranged from one to three tablets four times a day. Patients who were included in this study had back pain for more than two months and were on a stable (not changing) dose of a non-steroidal anti-inflammatory drug (NSAID) for at least two weeks before the start of the study. *[Confidential information related to this study, including average final doses of study medication, was removed at the manufacturer's request.]* Approximately 50% of patients stopped taking part in the study over the 12 weeks.
- BUP4009 with 135 patients was a 12-week-long study in which patients and doctors knew which medication was being used. This study looked to see if BuTrans was not worse than tramadol controlled release (CR) tablets (also called Zytram XL). Dosages could be adjusted at any time during the study. Allowable dosages of BuTrans ranged from a 5 mg to a 20 mg patch applied once every seven days. Allowable dosages of tramadol CR ranged from 75 mg to 200 mg taken twice daily. Patients who took part in the study had moderate to severe

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pain from osteoarthritis of the hip and/or knee, with ongoing pain despite using acetaminophen (also called Tylenol) 4 grams per day over a one-week period before the study. Average doses of medication during the study were between 10 mg and 15 mg per week for BuTrans and 300 mg per day for tramadol CR. Approximately 26% of patients stopped taking part in the study over the 12 weeks.

Patients who started BUP3015 had already confirmed before the study started that they improved with and were able to tolerate BuTrans; therefore, the results for this study are likely biased in favour of BuTrans. All studies had high numbers of patients stopping participation in the study, which differed depending on which medication they were using; this could have affected the accuracy of the results.

Outcomes

Outcomes were defined in advance in the CDR review protocol. Of these, the Committee discussed the following: pain intensity, quality of life, ability to function, stopping participation in the study, side effects, and stopping participation in the study because of side effects.

The main purpose of all three studies was to measure 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 average pain varied between the studies, 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 – average weekly BS-11 pain score, collected in subject diaries every evening for average pain during the day. BuTrans would be considered not worse than tramadol CR if the difference between the two medications was less than 1.5 boxes on the BS-11 scale.

Other results noted to be of importance to patients – such as ability to function and quality of life – were considered by the Committee. Data on these results were available from the reviewed studies; however, none of the reviewed studies specifically examined patients' ability to remain at or return to work.

Results

Efficacy or Effectiveness

- Because of the high percentage of patients stopping participation in the studies, and also because stopping participation differed depending on which treatment was received, the Committee looked at the following analyses of pain scores compared with the start of the study. In studies BUP3015 and BP96-0604, they took the data from the patients at study start and included this in the final result for patients who stopped participating. In study BUP4009, they looked at just the data of the patients who completed the study following study rules.
- In BUP3015, both BuTrans 20 mg and oxycodone IR lowered pain more than BuTrans 5 mg (average differences in pain score compared with BuTrans 5 mg of –0.60 and –0.84 for BuTrans 20 mg and oxycodone IR, respectively). Testing of the difference between BuTrans 20 mg and oxycodone IR was not done.

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- In BP96-0604, BuTrans reduced pain more than placebo (average difference in pain score of -0.97). [Details regarding the comparison of oxycodone plus acetaminophen with placebo were removed at the manufacturer's request.] There was no real difference between BuTrans 20 mg and oxycodone plus acetaminophen regarding pain reduction.
- In BUP4009, it was found that BuTrans was not worse than tramadol CR.
- In BUP3015 and BP96-0604, small improvements in the Oswestry Disability scores, which were not likely to make an important difference for patients, were seen for all treatments.
- Few comparisons of quality-of-life measures were reported in the studies, and the importance of any differences for patients is not known.

Harms (Safety and Tolerability)

- In all studies, stopping participation due to side effects occurred frequently, regardless of which analgesic was received.
- The percentage of patients who had a side effect was similar between BuTrans 20 mg and other analgesic medications.
- Only one case of respiratory depression (decreased breathing) was reported, and involved a patient in BUP3015 receiving BuTrans 5 mg.

Cost and Cost-Effectiveness

The manufacturer submitted an economic analysis comparing the price of BuTrans to oxycodone CR, based on the assumption of similar effectiveness and harms. No studies comparing BuTrans with oxycodone CR were available; therefore, the manufacturer relied on data from other studies. The manufacturer assumed that a 300 mg dose of codeine CR was equal to BuTrans 5 mg.

Based on recommended doses, the daily cost of BuTrans (5 mcg per hour, \$1.73; 10 mcg per hour, [confidential information removed at the manufacturer's request]; 20 mcg per hour, [confidential information removed at the 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 (also called Jurnista, \$2.02 to 4.03), fentanyl patch (also called Duragesic, \$1.22 to \$4.02), and tramadol CR (also called Zytram XL, \$1.60 to \$4.00). It is more expensive compared to codeine CR (also called Codeine Contin), hydromorphone CR (also called Hydromorph Contin), and sustained release morphine products.

Patient Input Information:

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

- The effect of pain on life satisfaction and the ability to perform work and daily activities are important for patients. Sleep disturbances and psychological distress due to pain, and gastrointestinal side effects of pain medications, are also of concern.
- Patient expectations for BuTrans transdermal patch are related to its unique drug delivery method (transdermal) compared to oral medications, and include less peaks and valleys of pain relief, an improved ability to stay with the treatment schedule, and less gastrointestinal irritation. Patients said that the transdermal method of delivery may decrease the abuse and misuse of opioids.

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Other Discussion Points:

- The Committee considered whether there was enough evidence to recommend listing BuTrans for patients who can't take medications by mouth and/or who have trouble giving themselves medications. However, none of the reviewed studies looked at the safety and effectiveness of BuTrans in these types of patients. Also, none of the reviewed studies specifically included patients who did not respond to, or could not tolerate, the effects of other more commonly used opioid analgesics.
- The Committee discussed the manufacturer's suggestion that BuTrans may be better than other opioid analgesics for elderly patients because the dose of BuTrans does not have to be reduced in patients with kidney problems. However, the Committee noted that only a small percentage of patients in the reviewed studies were older than 75 years of age, and the studies didn't report if the patients had kidney problems. Therefore, there is not much evidence of the effectiveness and safety of BuTrans compared with other opioid analgesics in these types of patients.
- If respiratory depression (difficulty breathing) occurs with BuTrans, it cannot be easily reversed with medication because it is hard to stop the effect of the drug, until it wears off naturally.

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:

The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed

information are advised to refer to the technical version available in the [CDR Drug Database](#) on the CADTH website (www.cadth.ca).

Background on CEDAC

CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has requested the deletion of confidential information.