CDEC FINAL RECOMMENDATION

FENTANYL CITRATE SUBLINGUAL TABLETS
(Abstral – Paladin Labs Inc.)
Indication: Management of Breakthrough Cancer Pain

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that fentanyl citrate sublingual tablets not be listed at the submitted price.

Reasons for the Recommendation:
1. At the submitted price, the cost of fentanyl citrate sublingual tablets greatly exceeds that of other available oral opioids.
2. There are no randomized controlled trials (RCTs) directly comparing fentanyl citrate sublingual tablets with other less costly opioids available for the management of breakthrough cancer pain.

Of Note:
Based on a review of the clinical evidence, the Committee felt that a reduced price would increase the likelihood of a recommendation to “list” or “list with criteria”.

Background:
Fentanyl citrate sublingual tablets have a Health Canada indication only for the management of breakthrough pain in patients with cancer, aged 18 years and older, who are already receiving, and who are tolerant to, opioid therapy for their persistent baseline cancer pain. Patients considered opioid tolerant are those who are taking at least 60 mg per day morphine equivalents for a week or longer. Fentanyl is a pure μ-opioid receptor agonist.

Fentanyl citrate sublingual tablets are available in the following strengths: 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg. The Health Canada–approved dose includes an initial dose of 100 mcg for all patients. If adequate analgesia is not obtained with the first 100 mcg, dose escalation in a stepwise manner over consecutive breakthrough episodes should continue until adequate analgesia with tolerable side effects is achieved. Doses higher than 800 mcg should not be used. Single doses should be separated by at least two hours and should be used only once per breakthrough cancer pain episode; i.e., fentanyl citrate sublingual tablets should not be re-dosed within an episode.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of fentanyl citrate sublingual tablets and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR Call for Patient Input.

No RCTs met the inclusion criteria for the CDR systematic review, as there were no RCTs comparing fentanyl citrate sublingual tablets with other immediate-release opioids or other fentanyl formulations. The Committee considered a summary of information relevant to fentanyl citrate sublingual tablets, prepared by the CDR, which included (i) trials of oral transmucosal fentanyl products that did not meet the CDR systematic review protocol, (ii) pharmacokinetics, (iii) abuse potential, and (iv) additional harms.

Summary of Findings
CDR identified eight trials that provided efficacy and harms data for fentanyl citrate sublingual tablets and other oral transmucosal fentanyl products. Four studies in cancer patients examined fentanyl citrate sublingual tablets: two were double-blind RCTs comparing fentanyl citrate sublingual tablets with placebo, and two studies did not include a comparator. The remaining four studies were RCTs that compared other oral transmucosal fentanyl products (oral transmucosal fentanyl citrate, Actiq, and fentanyl buccal tablet, Fentora) with other opioids; all trials specifically enrolled cancer patients, with the exception of one trial that included patients with chronic pain not limited to cancer.

Results from the aforementioned studies suggest that breakthrough pain intensity in cancer patients is significantly lowered in patients treated with fentanyl citrate sublingual tablets compared with placebo, and that other oral transmucosal fentanyl products are superior to oral morphine and oxycodone, but not intravenous (IV) morphine, for relief of breakthrough cancer pain. Results from one non-comparative trial reported that time to first notable analgesic effect with fentanyl citrate sublingual tablets was within five minutes or less for 68% of breakthrough pain episodes, and within 10 minutes or less for 83% of episodes. The most commonly observed adverse events with fentanyl citrate sublingual tablets were those considered typical of opioid treatment, including nausea and vomiting.

The pharmacokinetic profile of fentanyl citrate sublingual tablets is very similar to that of other oral transmucosal fentanyl preparations in humans, although these drugs have marked inter-individual variations. The time to maximal concentration is longer for oral transmucosal fentanyl products than for an IV infusion of fentanyl.

Although no data regarding the abuse potential of fentanyl citrate sublingual tablets compared with other fentanyl delivery systems were identified, sublingual fentanyl is expected to have a high abuse potential, similar to other rapid-acting opioid formulations.

Limited harms data are available for fentanyl citrate sublingual tablets, but the potential for serious adverse events with fentanyl due to respiratory depression, hypotension, and shock is well known. The Periodic Safety Update Reports have reported episodes of life-threatening swelling/oedema of the tongue; the manufacturer continues to monitor for such events.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-effectiveness analysis comparing fentanyl citrate sublingual tablets with immediate-release morphine tablets for the treatment of breakthrough cancer pain. The outcome measure examined in the cost-effectiveness analysis was the incremental cost per additional minute of breakthrough cancer pain control achieved. Efficacy data were obtained from a naive indirect comparison of four studies that estimated the time of onset of adequate pain reduction in patients using fentanyl citrate sublingual tablets or immediate-release morphine. The manufacturer reported an incremental cost per additional minute of pain relief of $0.85 and cited willingness-to-pay estimates reported in the published literature for various types of pain to support the cost-effectiveness of fentanyl citrate sublingual tablets.

The assessment of the cost-effectiveness analysis of fentanyl citrate sublingual tablets was limited by the lack of comparative clinical evidence relative to other agents to treat breakthrough cancer pain, and the difficulty in interpreting the measure used by the manufacturer for its cost-effectiveness ratio (cost per additional minute of breakthrough cancer pain control achieved).

The cost of fentanyl citrate sublingual tablets ranges from $10.60 to $30.29 per episode (100 mcg to 800 mcg). Assuming a patient experiences between one and four episodes of breakthrough pain per day, the cost would range from $10.60 to $121.16 per day, which is higher than the daily cost of oral immediate-release formulations of morphine ($1.15 to $2.58), oxycodone ($0.71 to $1.74), and hydromorphone ($0.57 to $1.34).

Other Discussion Points:

- The Committee recognized the need for rapid-acting, easily administered, and well-tolerated opioid formulations suitable for managing breakthrough cancer pain in the outpatient setting.
- There are no head-to-head RCTs of fentanyl citrate sublingual tablets, thus there are no data to support a price premium over that of other available oral opioid formulations.
- The manufacturer reported that estimates of incremental cost per additional minute of pain relief (range of $0.54 to $1.07) were much lower than amounts of willingness to pay for acute pain episodes relief or avoidance ($36.86 to $68.84) based on published studies in various types of pain. The Committee noted that the willingness-to-pay estimates (based on vaccine injection, post-surgical pain) reflect different severity and frequency of pain episodes, and may not be generalizable to breakthrough cancer pain.
- The Committee considered the abuse potential for fentanyl citrate sublingual tablets to be considerable.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

November 16, 2011 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest:
None

About this Document:
CDEC 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 CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC 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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