Canadian Drug Expert Committee
Final Recommendation – Plain Language Version

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

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that Abstral, which is also called fentanyl citrate sublingual (under the tongue) tablets, not be listed by Canada's publicly funded drug plans at the submitted price for the management of breakthrough cancer pain.

Reasons for the Recommendation:
1. At the submitted price, the cost of Abstral greatly exceeds that of other available oral (taken by mouth) opioids.
2. There are no well-designed medical studies comparing Abstral with other less costly opioids available for the management of breakthrough cancer pain.

Of Note:
Based on a review of the evidence, the Committee felt that a lower price would increase the chance of a recommendation to "list" or "list with criteria".

Background:
Abstral belongs to a class of drugs called opioids. Opioids are the strongest pain medicines available. Abstral is approved by Health Canada for adults aged 18 years and older, for the treatment of the sudden flares of pain that can occur unexpectedly while the patient is taking regular doses of opioid painkillers for constant cancer pain. The sudden flares of pain are described as "breakthrough pain" because they happen or "break through" the regularly taken opioid painkillers that address the constant cancer pain, and they usually last for a short while. Abstral is only for use by patients who have already been taking 60 mg of morphine per day (or the equivalent) for a week or longer.

Abstral is a tablet that is placed under the tongue, where it will dissolve rapidly to deliver fentanyl quickly into the bloodstream.

Abstral 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 a starting dose of

100 mcg for all patients. If the medication has not lowered the pain enough with the first 100 mcg dose, the dose should be increased with each breakthrough pain episode until the pain is controlled (as long as the side effects are not too strong). Doses above 800 mcg should not be used. Single doses should be given at least two hours apart and should only be used once per breakthrough cancer pain episode, that is, Abstral should not be given more than once during any one episode of breakthrough pain.

Summary of CDEC 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 Abstral and a review of the economic information prepared by the manufacturer of Abstral. No patient groups responded to the CDR Call for Patient Input.

No medical studies met the CDR review requirements, because there were no well-designed medical studies that compared Abstral with other fast-acting opioids or other pain-relieving products that contain fentanyl. The Committee reviewed a summary of information relevant to Abstral, prepared by the CDR, which included: (i) studies of oral transmucosal (absorbed through the mouth lining) fentanyl products that did not meet the CDR review requirements, (ii) pharmacokinetics (how the drug is absorbed, where it works, and how it is broken down and gotten rid of by the body), (iii) the potential for abuse, and (iv) additional harms.

Summary of Findings
CDR identified eight medical studies that provided information on the effectiveness and harms of either Abstral or other oral transmucosal fentanyl products. Four studies of patients with cancer looked at Abstral: two compared Abstral with placebo (a tablet containing no active medication) and two studies did not compare Abstral with any other medication. The other four studies compared other oral transmucosal fentanyl products (called Actiq and Fentora) with other opioids; all studies were done with patients with cancer, except for one study that included patients with long-term pain that was not necessarily from cancer.

Results from these studies suggest that breakthrough pain in patients with cancer is significantly lessened with Abstral compared with placebo, and that other oral transmucosal fentanyl products are better than oral morphine and oxycodone, but not better than intravenous (given into the vein) morphine, for the relief of breakthrough cancer pain. Results from one study (which did not compare Abstral to other medication) found that Abstral started having a noticeable painkilling effect within five minutes or less for 68% of breakthrough pain episodes, and within 10 minutes or less for 83% of episodes. The most commonly seen side effects with Abstral were those usually found with opioid treatment; for example, nausea and vomiting.

The pharmacokinetics of Abstral are similar to that of other oral transmucosal fentanyl treatments in humans, although there can be noticeable differences from person to person. It takes longer for fentanyl to reach its highest blood concentration when it is given as an oral transmucosal product compared with when it is given intravenously.

Although no information about the abuse potential of Abstral compared with other fentanyl products was found, Abstral is expected to have high abuse potential similar to other fast-acting opioid formulations.

There is not a lot of information about the harms of Abstral, but the possibility of serious side effects from fentanyl, such as difficulty breathing, low blood pressure, and shock (severe low blood pressure with the loss of consciousness and not enough blood flow to vital organs) is well known. The Periodic Safety Update Reports have reported episodes of life-threatening swelling of the tongue; the manufacturer continues to monitor for such events.

Cost and Cost-Effectiveness

The manufacturer submitted economic information to compare Abstral with immediate-release morphine tablets for the treatment of breakthrough cancer pain, to evaluate the health benefit. The outcome of interest used in the manufacturer's economic analysis was the additional cost to get an additional minute of relief from breakthrough cancer pain. Data for the manufacturer's analysis came from comparing the results of four studies that estimated the time to get good pain relief from either Abstral or immediate-release morphine. The manufacturer reported that Abstral would cost an additional $0.85 for each additional minute of pain relief, and indicated that patients consider this to be good value for money, based on studies done in various types of pain.

The review of the manufacturer's economic information was difficult because of the lack of studies comparing Abstral with other opioids used for breakthrough cancer pain, and the challenge of interpreting the measurement used by the manufacturer to assess the cost-effectiveness of Abstral; that is the cost per additional minute of breakthrough cancer pain relief.

The cost of Abstral 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 understood the need for fast-acting, easily given, and well-tolerated opioid formulations suitable for treating breakthrough cancer pain in the outpatient setting.
- There are no studies comparing Abstral with other pain relieving medications; thus, there is no evidence to support paying more for Abstral than for other oral opioid formulations.
- The manufacturer reported that the estimates of the extra cost per additional minute of pain relief (range of $0.54 to $1.07) were much lower than how much people are willing to pay in order to treat or avoid pain ($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, pain after surgery), are different situations and may not be the same for breakthrough cancer pain.
- The Committee felt that the abuse potential of Abstral is 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
The information contained within this plain language version of the CDEC Recommendation about this drug is based on the information found within the corresponding technical version of the CDEC Recommendation.

In making its recommendation, CDEC 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 CDEC
CDEC 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. CDEC 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, CDEC 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 CDEC deliberations.

The CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient, nor is it intended to replace professional advice. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

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 not requested the deletion of any confidential information.