CDEC FINAL RECOMMENDATION

FENTANYL CITRATE BUCCAL SOLUBLE FILM RESUBMISSION
(Onsolis – Meda Valeant Pharma Canada Inc.)
Indication: Pain (Breakthrough), Cancer (Adults)

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

Reasons for the Recommendation:
1. At the submitted price, the cost of fentanyl citrate buccal soluble film greatly exceeds that of other available oral opioids.
2. There are no randomized controlled trials (RCTs) directly comparing fentanyl citrate buccal soluble film with other less costly opioids 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 buccal soluble film has a Health Canada indication for the management of breakthrough pain in cancer patients 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 buccal soluble film is available in the following strengths: 200 mcg, 400 mcg, 600 mcg, 800 mcg, and 1,200 mcg. The Health Canada–approved dose includes an initial dose of 200 mcg. If adequate analgesia is not reached after the first dose, the dose may be increased by 200 mcg in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. Doses greater than 1,200 mcg should not be used. Single doses should be separated by at least four hours and should be used only once per breakthrough cancer pain episode; i.e., fentanyl citrate buccal soluble film should not be redosed within an episode.

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Submission History:
Fentanyl citrate buccal soluble film was originally submitted to the Common Drug Review (CDR) in May 2011. The submission was withdrawn by the manufacturer and subsequently resubmitted in September 2011.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the CDR: a systematic review of RCTs of fentanyl citrate buccal soluble film and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR Call for Patient Input.

No RCTs met the minimum inclusion criteria for the CDR systematic review, as there were no RCTs comparing fentanyl citrate buccal soluble film with other immediate-release opioids or other fentanyl formulations. The Committee considered a summary of information relevant to fentanyl citrate buccal soluble film, 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:
The CDR identified five trials that provided relevant efficacy and harms data for fentanyl citrate buccal soluble film and other oral transmucosal fentanyl products. One RCT compared fentanyl citrate buccal soluble film with placebo. Results of this trial suggest that breakthrough pain intensity in cancer patients was statistically significantly reduced compared with baseline, and was superior to that achieved in the placebo group. The most commonly reported adverse events were typical of opioid therapy, including nausea, vomiting, and dizziness. No additional insight into the harms profile of fentanyl citrate buccal soluble film was added to what is commonly known about fentanyl products.

The remaining four trials identified were RCTs that compared other oral transmucosal fentanyl products (oral transmucosal fentanyl citrate, Actiq, and fentanyl buccal tablets, Fentora) with other opioids; all trials specifically enrolled cancer patients, with the exception of one trial that enrolled patients with chronic pain not limited to cancer. Results from these trials suggest that oral transmucosal preparations of fentanyl are superior to oral morphine and oxycodone, but not intravenous morphine, for the relief of breakthrough cancer pain.

The pharmacokinetic profile of fentanyl citrate buccal soluble film is very similar to that of other oral transmucosal fentanyl preparations in humans, although these drugs have marked interindividual variations. The time to maximal concentration is longer for oral transmucosal fentanyl products than for an intravenous infusion of fentanyl.

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

Limited harms data are available specifically for fentanyl citrate buccal soluble film. However, serious adverse events that included respiratory depression, deep vein thrombosis, subdural hematoma, and dyspnea were identified in Periodic Safety Update Reports and are listed in the product monograph.

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Cost and Cost-Effectiveness:
The manufacturer submitted a cost-minimization analysis comparing fentanyl citrate with other agents currently available in Canada for breakthrough pain in patients with cancer, based on the assumption of similar safety and efficacy. No RCTs were conducted comparing fentanyl citrate with any of the comparators, nor was an indirect comparison provided. The analysis was further limited by the lack of comparative clinical evidence and information on dose equivalence.

Based on recommended doses (up to four 200 mcg, 400 mcg, 600 mcg, 800 mcg, or 1,200 mcg films per day) of fentanyl citrate, the daily cost ($12.00 to $65.40) is higher than the daily cost of 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 an effective, easily administered, and rapid-acting opioid formulation for the management of breakthrough cancer pain in the outpatient setting.
- The Committee considered the abuse potential for fentanyl citrate buccal soluble film to be considerable.
- There are no head-to-head RCTs of fentanyl citrate buccal soluble film, thus there are no data to support a price premium over other available oral opioid formulations.

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.

January 18, 2012 Meeting

Regrets:
None

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*.

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