CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

Fentanyl buccal/sublingual effervescent tablet (Fentora — Teva Canada Innovation) Indication: Breakthrough cancer pain (adults)

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that Fentora not be reimbursed for the management of breakthrough pain in patients with dysphagia or a lack of adequate pain relief or intolerable opioid-related toxicities or adverse events or contraindication to morphine, oxycodone, or hydromorphone.

Reasons for the Recommendation:
1. There is no evidence available to evaluate the efficacy and safety of Fentora in the population specified in the request for reimbursement; specifically, patients with dysphagia and/or a lack of adequate pain relief and/or intolerable opioid-related toxicities or adverse events or contraindication to morphine, oxycodone, or hydromorphone.
2. There is no evidence that patients who are unable to achieve pain relief with the pain management strategies that are currently available would benefit from treatment with Fentora.

Background:
Fentora 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 continuous opioid therapy for their persistent baseline cancer pain. Fentora is available in multiple doses — 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg — as fentanyl citrate buccal/sublingual effervescent tablets.

Summary of CDEC Considerations
CDEC considered the following evidence: a systematic review of randomized controlled trials (RCTs) of Fentora and a critique of the manufacturer's pharmacoeconomic evaluation.

Patient Input Information:
No patient input was received for this submission.

Clinical Trials

The evidence for this review was drawn from two RCTs — Study 14 (N = 77) and Study 3039 (N = 87) — each of which compared Fentora with placebo. Each trial comprised a screening period, an open-label (OL) dose titration period, and a double-blind (DB) treatment period. During the treatment period, participants received 10 study drug tablets — seven were Fentora, and three were placebo — in one of 18 random sequences. Both studies enrolled opioid-tolerant adults with cancer-related pain.

Outcomes

The following outcomes were defined a priori in the CADTH Common Drug Review (CDR) systematic review protocol:

- Change in pain intensity
- Frequency of breakthrough pain episodes
- Change in health-related quality of life (HRQoL)
- Use of rescue medications
- Mortality, adverse events, serious adverse events (SAEs), withdrawals due to adverse events, and notable harms (dizziness, nausea, vomiting, constipation, somnolence, itchiness, respiratory depression, abuse, misuse, diversion).

The primary efficacy outcome in both studies was the summed pain intensity difference (SPID) through 30 minutes (sum of pain intensity difference [PID] at 15 and 30 minutes after administration of study drug) for Study 14, and 60 minutes (time-weighted sum of PID at five, 10, 15, 30, 45, and 60 minutes) for Study 3039.

Efficacy

In Study 14, Fentora was associated with statistically significant reductions in mean SPID and PID compared with placebo at 15, 30, 45, and 60 minutes after study drug administration. In Study 3039, Fentora was associated with a statistically significant reduction in mean SPID compared with placebo at 30, 60, 90, and 120 minutes, and in mean PID at 10, 15, 30, 45, 60, 90, and 120 minutes after study drug administration. Across Studies 14 and 3039, the magnitude of the between-group difference in reduction in mean PID ranged from 0 (on a 0 to 10 scale) at five minutes to 1.9 at 90 and 120 minutes after study treatment.

In Study 14, compared with placebo, a statistically greater percentage of breakthrough pain episodes treated with Fentora were characterized by ≥ 33% improvement in pain intensity at 15 minutes (13% versus [vs.] 9%), 30 minutes (48% vs. 29%), 45 minutes (71% vs. 44%), and 60 minutes (75% vs. 48%) after study drug administration. In the same study, compared with placebo, a statistically greater percentage of breakthrough pain episodes treated with Fentora were characterized by ≥ 50% improvement in pain intensity at 30 minutes (24% vs. 16%), 45 minutes (51% vs. 25%), and 60 minutes (64% vs. 35%) after study drug administration. In Study 3039, compared with placebo, a statistically greater percentage of breakthrough pain episodes treated with Fentora were characterized by ≥ 33% improvement in pain intensity at 10 minutes (16% vs. 10%), 15 minutes (29% vs. 14%), 30 minutes (51% vs. 26%), 45 minutes (65% vs. 31%), 60 minutes (69% vs. 33%), 90 minutes (73% vs. 36%), and 120 minutes (74% vs. 38%) after study drug administration. In the same study, compared with placebo, a statistically greater percentage of breakthrough pain episodes treated with Fentora were characterized by ≥ 50% improvement in pain intensity at 10 minutes (7% vs. 4%), 15 minutes (18% vs. 8%), 30 minutes

(38% vs. 15%), 45 minutes (53% vs. 20%), 60 minutes (59% vs. 22%), 90 minutes (63% vs. 26%), and 120 minutes (66% vs. 28%) after study drug administration.

In Study 14, rescue medications were used for 117 of 493 (23.7%) breakthrough pain episodes for which Fentora was used, compared with 105 of 208 (50.3%) episodes for which placebo was used in the treatment period, resulting in an odds ratio (OR) (95% confidence interval [CI]) of 3.25 (2.23 to 4.72). In Study 3039, rescue medications were used for 53 of 493 (10.8%) breakthrough pain episodes for which Fentora was used, compared with 67 of 223 (30.0%) episodes for which placebo was used in the treatment period, resulting in an OR (95% CI) of 3.58 (2.23 to 5.75).

Neither trial evaluated the effects of Fentora on the frequency of breakthrough pain episodes or HRQoL, both of which were pre-specified outcomes of interest to the CDR team. In addition, neither trial considered the effects of the study treatments in palliative or non-palliative care patients, both of which were populations of interest to the CDR team. Further, neither trial evaluated the effects of Fentora specifically among participants with dysphagia or those who had lack of pain relief and/or intolerable opioid-related toxicities or adverse events or contraindication to other IR opioids — both of which were included in the reimbursement request.

In the absence of direct evidence of the relative efficacy of Fentora compared with other active treatment options, the manufacturer submitted one network meta-analysis (NMA) that evaluated the efficacy of Fentora against morphine sulfate immediate release (MSIR), another fentanyl buccal tablet (FBT/2), fentanyl sublingual tablet (FST), fentanyl buccal soluble film (FBSF), fentanyl sublingual spray, fentanyl Ethypharm (FE), fentanyl pectin nasal spray, intranasal fentanyl spray (INFS), and oral transmucosal fentanyl citrate (OTFC). The results were largely inconsistent but suggested that Fentora might be associated with statistically significant reductions in PID vs. FBT/2 at 30 minutes; vs. FBSF and MSIR at 45 minutes; and vs. FBT/2, FBSF, FE, FST, and MSIR at 60 minutes. A published NMA found that INFS was associated with statistically significant reductions in PID versus Fentora at 15 minutes and 30 minutes, but not at 45 and 60 minutes. Two other NMAs found no statistically significant reductions in PID with Fentora versus MSIR at 15, 30, 45, and 60 minutes, and one of them also demonstrated no statistically significant differences versus OTFC or MSIR at 15, 30, 45, and 60 minutes.

Harms (Safety and Tolerability)

At least 66% of the overall study population in each of the two trials experienced a treatment-emergent adverse event (TEAE). The rate of TEAEs, however, appeared to be higher in Study 14 than in Study 3039 during the OL dose titration period and the DB treatment period: 66% vs. 47% in the titration period and 61% vs. 55% in the treatment period. The overall rates of SAEs across the two studies were approximately equal — 11% in Study 14; 9% in Study 3039 — and all of the events were considered not related or unlikely to be related to the study treatment, according to the manufacturer. Of the notable harms that were reported, specifically dizziness, nausea, vomiting, and somnolence, a numerically greater percentage of participants in Study 14 were affected than in Study 3039: 22% vs. 11% for dizziness; 22% vs. 13% for nausea; 11% vs. 6% for vomiting; 10% vs. 0% for somnolence. The occurrence of constipation was approximately equal (8% vs. 6%) across the two studies. There were no reported cases of respiratory depression in either study. Neither of the studies reported on abuse, misuse, or diversion. The manufacturer conducted a long-term OL safety study of Fentora that found no

new safety concerns relative to the patients who were in Studies 14 or 3039, although several methodological limitations necessitate caution in interpreting the findings. Across the three studies — Studies 14, 3039, and the long-term safety study — a total of 73 (20%) participants died, although all deaths were attributed to disease progression.

Cost and Cost-Effectiveness

Fentora is available as 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg tablets at a manufacturer-submitted price of $10.89 per tablet for all strengths. The maximum recommended dose is 800 mcg per episode of breakthrough cancer pain (BTCP) and use should be limited to a maximum of four episodes of BTCP per day. As such, Fentora costs $10.89 to $43.56 daily. This cost does not account for initial dose titration required to determine the dose for adequate pain relief.

The manufacturer submitted a cost-utility analysis comparing Fentora to usual care (defined as MSIR 20 mg oral tablet) for the management of BTCP among cancer patients who met the reimbursement request criteria: lack of adequate relief or intolerable toxicity, adverse events, or contraindication to short-acting/IR opioids (morphine, oxycodone, hydromorphone) and/or dysphagia. The analysis was based on a decision tree with a time horizon of 181.5 days, undertaken from the perspective of the Canadian publicly funded health care system. Comparative treatment effectiveness data (defined by pain intensity reduction from baseline) were derived from a manufacturer-commissioned NMA. The manufacturer reported that, compared with usual care, use of Fentora was associated with an incremental cost-utility ratio (ICUR) of $91,592 per quality-adjusted life-year (QALY).

CDR identified the following key limitations with the manufacturer's economic submission:

- Assumption that patients on MSIR incurred the costs of MSIR but experienced the same intensity of pain as patients taking placebo in the phase III pivotal trials of Fentora. This assumption biases results in favour of Fentora.
- Uncertainty regarding the duration of treatment benefit with Fentora relative to the length of a BTCP episode. The manufacturer assumed that patients experienced the benefits of Fentora over 24 hours using treatment-specific BTCP utilities. This assumption is unsupported by data and biases the results in favour of Fentora.
- Uncertainty with respect to daily frequency of BTCP episodes. Specifically, the manufacturer's assumption of three episodes per day was considered to be an underestimate.
- Concerns regarding the clinical evidence used in the cost-utility analysis, specifically the limited generalizability of the results from the phase III pivotal trials to the population in clinical practice, due to high dropout rates and stringent inclusion and exclusion criteria.

Based on reanalyses to account for some of the above limitations — use of MSIR efficacy values rather than placebo values for MSIR, assuming that patients experienced four BTCP episodes per day, and that the benefits of Fentora lasted for the duration of the BTCP episode (one hour) and one additional hour beyond that (i.e., duration of treatment effect was assumed to be two hours rather than 24) — CDR estimated the ICUR for Fentora vs. MSIR to be greater than $617,000 per QALY. A price reduction of 85% is necessary to achieve an ICUR of $50,000 per QALY. However, the cost-utility analysis used data reflecting a patient population aligned

with the Health Canada indication, and results may not be generalizable to the specific population for which reimbursement is requested.

Discussion Points:

- The Committee discussed the potential for the diversion and misuse of Fentora.
- Although CADTH received no input from patient groups for this review, the Committee did discuss with two clinical experts the situations and needs of cancer patients who require relief from breakthrough pain, and the treatment options that are currently available. A public member also summarized a letter sent to CADTH (not specifically related to this review) by the Canadian Society of Palliative Care Physicians about the effectiveness of opioids, especially fast-acting ones, in many of their patients.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

January 18, 2017 Meeting

Regrets:

None

Conflicts of Interest:

None

About This Document:

CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. 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.

The CDEC recommendation or record of advice 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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