Common Drug Review
Clinical Review Report

March 2017

Drug	Fentanyl (FENTORA)
Indication	Management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to continuous opioid therapy for their persistent baseline cancer pain.
Reimbursement request	Management of breakthrough pain in advanced cancer patients 18 years of age or older with the underlying pain adequately managed using a continuous opioid therapy (persistent baseline cancer pain) and one or more of: • Lack of adequate pain relief and/or intolerable opioids related toxicities or adverse events or contraindication to any one of the following short acting/immediate release opioids: morphine, oxycodone, hydromorphone and/or • Difficulty to swallow (dysphagia)
Dosage form (s)	100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg (buccal/sublingual effervescent tablet)
NOC date	21/11/2013
Manufacturer	Teva Canada Innovation

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TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
ATC	around-the-clock
CrI	credible interval
CI	confidence interval
CDR	CADTH Common Drug Review
COPD	chronic obstructive pulmonary disease
DB	double-blind
DIC	deviance information criterion
ECOG	Eastern Cooperative Oncology Group
FBSF	fentanyl buccal sublingual film
FBT	fentanyl buccal tablet
FBT/2	fentanyl buccal tablet #2
FDA	Food and Drug Administration
FE	fentanyl Ethypharm
FPNS	fentanyl pectin nasal spray
FSS	fentanyl sublingual spray
FST	fentanyl sublingual tablet
GMP	global medication performance
HRQoL	health-related quality of life
IDC	indirect comparison
INFS	intranasal fentanyl spray
IR	immediate-release
ITT	intention-to-treat
LOCF	last observation carried forward
MSIR	morphine sulfate immediate-release
NA	not applicable
NMA	network meta-analysis
OL	open-label
OR	odds ratio
OTFC	oral transmucosal fentanyl citrate
PI	pain intensity
PID	pain intensity difference
PR	pain relief
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SPID	summed pain intensity difference

TEAE	treatment-emergent adverse event
TOTPAR	total pain relief
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Breakthrough pain is described as a transitory exacerbation of pain that occurs despite a background of adequately controlled pain. More than half of patients with cancer pain likely experience breakthrough pain. On average, patients may experience between four to six episodes of breakthrough pain daily, and the mean duration of each episode is approximately 30 minutes. Breakthrough pain has a rapid onset that can reach peak intensity in as little as one minute. Patients have consistently reported that breakthrough cancer pain negatively affects their daily living activities and quality of life. Managing patients with breakthrough cancer pain commonly involves prescribing them short-acting opioids as rescue medications, including immediate-release (IR) morphine, oxycodone, and hydromorphone. Fentora is a fentanyl buccal/sublingual effervescent tablet, the principal therapeutic action for which is analgesia.

Indication under review
Management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to continuous opioid therapy for their persistent baseline cancer pain.
Reimbursement criteria requested by sponsor
Management of breakthrough pain in advanced cancer patients 18 years of age or older with the underlying pain adequately managed using a continuous opioid therapy (persistent baseline cancer pain) and one or more of: • Lack of adequate pain relief and/or intolerable opioid-related toxicities or adverse events or contraindication to any one of the following short acting / immediate release opioids: morphine, oxycodone, hydromorphone and/or • Difficulty to swallow (dysphagia)

The objective of this review was to perform a systematic review of the beneficial and harmful effects of Fentora 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.

Results and Interpretation

Included studies

The evidence for this review was drawn from two randomized controlled trials (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, patients received 10 study drug tablets — seven were Fentora and three were placebo — in one of 18 random sequences. 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 the study drug) for Study 14, and 60 minutes (time-weighted sum of PID at 5, 10, 15, 30, 45, and 60 minutes) for Study 3039. Of note, discussions with one of the consulting clinical experts indicated that SPID is not an outcome used to evaluate treatment response in routine clinical practice.

Relevant secondary efficacy outcomes included PID (reduction in mean PID and number of responder episodes with ≥ 33% and ≥ 55% improvement in pain intensity) and use of rescue medications, while relevant harms outcomes included mortality, adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and several notable harms. Both studies enrolled opioid-tolerant adults with cancer-related pain.

Of note, the numerous exclusion criteria imposed by the two studies and the substantial percentage of patients who withdrew from both studies restrict the clinical population to whom the results of the studies may be directly applied. In addition, several methodological limitations necessitate caution in interpreting the treatment effects, including uncertainty regarding the allocation concealment procedure, possible unblinding of study treatments, lack of adjustment for multiplicity for all secondary efficacy outcomes, limited exploration of the sensitivity of the results to the restricted randomization procedures, and lack of testing for carry-over effects.

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 (Table 1). 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 9%), 30 minutes (48% versus 29%), 45 minutes (71% versus 44%), and 60 minutes (75% versus 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% versus 16%), 45 minutes (51% versus 25%), and 60 minutes (64% versus 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% versus 10%), 15 minutes (29% versus 14%), 30 minutes (51% versus 26%), 45 minutes (65% versus 31%), 60 minutes (69% versus 33%), 90 minutes (73% versus 36%), and 120 minutes (74% versus 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% versus 4%), 15 minutes (18% versus 8%), 30 minutes (38% versus 15%), 45 minutes (53% versus 20%), 60 minutes (59% versus 22%), 90 minutes (63% versus 26%), and 120 minutes (66% versus 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 effects of Fentora on the frequency of breakthrough pain episodes or health-related quality of life, both of which were pre-specified outcomes of interest to the CADTH Common Drug Review (CDR) team. In addition, neither trial evaluated the effects of the study treatments between palliative care patients and non-palliative care patients, which were pre-specified subgroups of interest to the CDR team. Further, neither trial evaluated effects of Fentora specifically among patients with dysphagia or those who had lack of pain relief and/or intolerable opioid-related toxicities or AEs 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 IR (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). [redacted]. A published NMA found that INFS was associated with statistically significant reductions in PID versus Fentora at 15 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

At least 66% of the overall study population in each of the two trials experienced a treatment-emergent adverse event (TEAE) (Table 2). 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% versus 47% in the titration period and 61% versus 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, per the manufacturer. Of most notable harms that were reported, specifically dizziness, nausea, vomiting, and somnolence, a numerically greater percentage of patients in Study 14 were affected than those in Study 3039 — 22% versus 11% for dizziness; 22% versus 13% for nausea; 11% versus 6% for vomiting; 10% versus 0% for somnolence. The occurrence of constipation was approximately equal (8% versus 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 Studies 14 or 3039, although several methodological limitations necessitate caution in interpreting the findings. Across the three studies — Study 14, Study 3039, and the long-term OL safety study — a total of 73 patients (20%) died, although all deaths were attributed to disease progression.

Other Considerations

Discussions with one of the consulting clinical experts highlighted several implementation issues with respect to Fentora. First, given that there is no method to directly convert the doses of Fentora to oral morphine equivalent, the expert raised concerns about the potential for errors in administering the appropriate strength of Fentora, which could lead to an increase in potential harm to patients. Second, Fentora contains fentanyl — a Schedule 1 controlled substance in Canada — which is liable to a similar level of abuse potential as other opioids, ultimately leading to fatal overdoses. Indeed, the spouse of a participant enrolled in a chronic non-cancer pain study of Fentora apparently pilfered and self-administered the participant's Fentora, and died due to respiratory depression. While there is no

obvious reason to expect that fentanyl preparations such as Fentora would be subject to an increased risk of being abused or otherwise diverted compared with other IR opioid treatments, the manufacturer has developed a comprehensive Risk Minimization Action Plan (RiskMAP) that outlines plans for "appropriate intervention" should a concerning safety signal develop in the post-marketing period in the US. Third, both experts consulted by the CDR team indicated that it would be extremely unusual for patients to have a contraindication to IR morphine, oxycodone, or hydromorphone but be able to tolerate Fentora, as the reimbursement request suggests.

Conclusions

Results from two RCTs — Study 14 (N = 77) and Study 3039 (N = 87) — suggest that, when compared with placebo, Fentora is associated with a statistically and clinically meaningful (as indicated by the responder episode analyses) improvement in PID as early as 10 minutes and lasting up to two hours after administration. Patients who were administered placebo were more likely to use rescue medication compared with Fentora-treated patients. Neither of the trials evaluated the effects of Fentora on the frequency of breakthrough pain episodes or health-related quality of life; nor did they assess its effects among patients with dysphagia or those who had lack of pain relief and/or intolerable opioid-related toxicities or AEs or contraindication to other IR opioids. The results of [redacted] published NMAs suggested that the analgesic effects of Fentora are similar to the effects of other opioids in managing breakthrough cancer pain. Data from Studies 14 and 3039 indicated that the safety profile of Fentora is consistent with that of other formulations of fentanyl and other opioids, and notable harms that were commonly reported among all patients in the two trials included dizziness, nausea, vomiting, and somnolence. There are no data to directly evaluate the relative safety of Fentora versus other active treatment options. Although fentanyl has a well-documented record of abuse, which is common also to other IR opioids, neither of the included studies reported on abuse, misuse, or diversion with Fentora. A long-term OL safety study of Fentora did not reveal any new safety concerns relative to Studies 14 or 3039.

TABLE 1: SUMMARY OF EFFICACY RESULTS

	Study 14		Study 3039	
	Fentora (n = 72)	Placebo (n = 72)	Fentora (n = 78)	Placebo (n = 78)
SPID				
Reduction at 15 minutes				
LSM (SE)	0.8 (0.06)	0.5 (0.08)	Not evaluated	
Difference (95% CI), *P* value[a]	**0.3[b] (NR) to *P* < 0.0001**			
Reduction at 30 minutes				
LSM (SE)	3.0 (0.12)	1.8 (0.18)	3.3 (0.1)	1.9 (0.2)
Difference (95% CI), *P* value[a]	**1.2[b] (0.8 to 1.6) to *P* = 0.0005**		**1.4[b] (1.1 to 1.8) to *P* < 0.0001**	
Reduction at 45 minutes				
LSM (SE)	6.3 (0.2)	3.6 (0.3)	Not evaluated	
Difference (95% CI), *P* value[a]	**2.7[b] (NR) to *P* < 0.0001**			
Reduction at 60 minutes				
LSM (SE)	10.2 (0.3)	5.8 (0.4)	9.8 (0.3)	5.0 (0.4)
Difference (95% CI), *P* value[a]	**4.4[b] (NR) to *P* < 0.0001**		**4.8 (3.9 to 5.6) to *P* < 0.0001**	
Reduction at 90 minutes				
LSM (SE)	Not evaluated		17.0 (0.4)	8.5 (0.6)
Difference (95% CI), *P* value[a]			**8.5[b] (7.0 to 9.9) to *P* < 0.0001**	
Reduction at 120 minutes				
LSM (SE)	Not evaluated		24.3 (0.6)	12.1 (0.9)
Difference (95% CI), *P* value[a]			**12.2[b] (10.2 to 14.2) to *P* < 0.0001**	
PID				
Baseline				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	6.9 (1.6)	6.9 (1.6)	6.4 (0.04)	6.4 (0.05)
Difference (95% CI), *P* value[c]	0.0[b] (NR) to *P* = 0.7319		0.0[b] (–0.15 to 0.10) to *P* = 0.7133	
Reduction at 5 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	Not evaluated		0.3 (0.03)	0.3 (0.04)
Difference (95% CI), *P* value[c]			0.0[b] (–0.06 to 0.14) to *P* = 0.4125	
Reduction at 10 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	Not evaluated		0.9 (0.04)	0.5 (0.06)
Difference (95% CI), *P* value[c]			**0.4[b] (0.20 to 0.48) to *P* < 0.0001**	
Reduction at 15 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	0.9 (1.1)	0.6 (0.9)	1.5 (0.06)	0.8 (0.09)
Difference (95% CI), *P* value[c]	**0.3[b] (NR) to *P* = 0.0029**		**0.7[b] (0.45 to 0.85) to *P* < 0.0001**	

	Study 14		Study 3039	
	Fentora (n = 72)	Placebo (n = 72)	Fentora (n = 78)	Placebo (n = 78)
Reduction at 30 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	2.3 (1.5)	1.4 (1.4)	2.4 (0.08)	1.3 (0.11)
Difference (95% CI), *P* value[c]	**0.9[b] (NR) to *P* < 0.0001**		**1.1[b] (0.83 to 1.35) to *P* < 0.0001**	
Reduction at 45 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	3.3 (1.8)	1.9 (1.6)	3.1 (0.08)	1.5 (0.12)
Difference (95% CI), *P* value[c]	**1.4[b] (NR) to *P* < 0.0001**		**1.6[b] (1.30 to 1.86) to *P* < 0.0001**	
Reduction at 60 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	4.0 (2.0)	2.3 (1.9)	3.4 (0.09)	1.7 (0.13)
Difference (95% CI), *P* value[c]	**1.7[b] (NR) to *P* < 0.0001**		**1.7[b] (1.45 to 2.04) to *P* < 0.0001**	
Reduction at 90 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	Not evaluated		3.6 (0.09)	1.7 (0.13)
Difference (95% CI), *P* value[c]			**1.9[b] (1.56 to 2.16) to *P* < 0.0001**	
Reduction at 120 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	Not evaluated		3.7 (0.09)	1.8 (0.13)
Difference (95% CI), *P* value[c]			**1.9[b] (1.55 to 2.16) to *P* < 0.0001**	

ANOVA = analysis of variance; CI = confidence interval; LSM = least squares mean; NR = not reported; PID = pain intensity difference; SD = standard deviation; SE = standard error; SPID = summed pain intensity difference.
Note: Statistically significant results are bolded.
[a] In Study 14, the LSM, SE of LSM, and *P* value were based on a repeated measures ANOVA with treatment, centre, and participant within centre as factors. In Study 3039, the *P* value was based on an ANOVA with treatment as a fixed factor and participant as a random factor.
[b] Calculated by the CADTH Common Drug Review clinical review team as difference between Fentora and placebo.
[c] In Study 14, the *P* value was based on a one-sample Wilcoxon signed rank test. In Study 3039, the *P* value was based on an ANOVA with treatment as a fixed factor and participant as a random factor.

TABLE 2: SUMMARY OF HARMS RESULTS

	Study 14	Study 3039
	Overall (N = 123)	Overall (N = 125)
Patients with > 0 TEAEs, n (%)	95 (77)	83 (66)
Patients with > 0 SAEs, n (%)	14 (11)	11 (9)
Withdrawals due to AEs, n (%)	15 (12)	19 (15)
Number of deaths, n (%)	7 (6)	8 (6)
Notable harms, n (%)		
Dizziness	27 (22)	14 (11)
Nausea	27 (22)	15 (13)
Vomiting	13 (11)	8 (6)
Constipation	10 (8)	7 (6)
Somnolence	12 (10)	0
Pruritus	NR	
Pruritus generalized		
Respiratory depression	0	
Abuse	NR	
Misuse		
Diversion		

AE = adverse event; DB = double-blind; NR = not reported; OL = open-label; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Breakthrough pain is described as a transitory exacerbation of pain that occurs despite a background of adequately controlled pain.[1] It can be spontaneous (unpredictable) or incidental (predictable), the latter of which can be volitional (initiated by a voluntary act), non-volitional (initiated by an involuntary act), or procedural (initiated by a therapeutic intervention). More than half of patients with cancer pain likely experience breakthrough pain, with one study suggesting that as many as 81% of patients might be affected.[2] On average, patients may experience between four and six episodes of breakthrough pain daily,[3] with one reported case of 3,600 episodes in a day.[4] Some reports suggest that the mean duration of each episode is approximately 30 minutes,[5,6] although the pain can last up to 60 minutes.[7] Breakthrough pain has a rapid onset that can reach peak intensity in as little as one minute.[1] Patients have consistently reported that breakthrough cancer pain negatively affects their daily living activities and quality of life.[8,9]

1.2 Standards of Therapy

One approach to managing patients with breakthrough cancer pain has been to increase their dosage of around-the-clock (ATC) opioids.[10] Doing so, however, increases the occurrence of opioid side effects, thus necessitating a careful assessment of the relative benefits of additional ATC analgesia.

Discussions with the two clinical experts consulted by the CADTH Common Drug Review (CDR) for this review, as well as consensus recommendations from a 2016 Canadian panel of experts,[1] indicated that the prevailing approach to managing patients with breakthrough cancer pain is to prescribe them short-acting opioids as supplemental (rescue) analgesics. The use of immediate-release (IR) opioids as rescue medications in combination with ATC opioids is thought to provide greater analgesia with fewer side effects.[10] In particular, the same opioids that are used as ATC medication may be prescribed as rescue medication; in Canada, according to the experts, these are likely to be one of IR morphine, oxycodone, or hydromorphone

In Canada, besides Fentora, only one treatment — Abstral (fentanyl sublingual tablet [FST]) — is indicated for the management of breakthrough cancer pain.[11] Abstral was reviewed by the CADTH Canadian Drug Expert Committee in 2011 and was recommended to "not be listed … at the submitted price."[12] To this end, both consulting clinical experts indicated that Abstral is not commonly used in routine clinical practice. Another treatment — Onsolis (fentanyl buccal soluble film [FBSF]) — was approved for this indication, but was withdrawn from the market prior to launch. Rescue opioids may also be given parenterally to manage breakthrough pain, with one expert indicating that subcutaneous administrations are most commonly used in routine practice today. In Canada, there are no national guidelines for the management of breakthrough cancer pain, although some provincial agencies briefly touch upon the topic.[10] For instance, Cancer Care Ontario recommends using the same opioids that are used as ATC medication to manage breakthrough pain at a dose that is 10% to 15% of the daily ATC dose, although it does not suggest specific analgesics.[13] It does not, however, recommend intramuscular medications for breakthrough pain, as they are "painful and unreliable."[13]

1.3 Drug

Fentora contains fentanyl, the principal therapeutic action for which is analgesia.[14] The precise mechanism of the analgesic action of fentanyl is unknown, although it is known to be a μ-opioid receptor agonist. Fentora is available in multiple doses — 100 mcg, 200 mcg, 400 mcg, 600 mcg, and

800 mcg as fentanyl citrate — as fentanyl buccal/sublingual effervescent tablets. Per the Health Canada product monograph, all patients starting treatment with Fentora must begin with titration from the 100 mcg dose. Patients who need to titrate to a higher dose can use two 100 mcg tablets with their next breakthrough pain episode; if this dosage is not successful, patients may use a total of four 100 mcg tablets. For doses above 400 mcg (i.e., 600 mcg and 800 mcg), Fentora must be titrated using multiples of the 200 mcg tablet. Once patients have been titrated to an effective dose of Fentora, they should use only one tablet per breakthrough pain episode. The maximum single dose should not exceed 800 mcg. Further, Fentora should only be used once per breakthrough cancer pain episode. If adequate pain relief is not achieved after use of Fentora, patients may use a rescue medication after 30 minutes. Patients must wait at least four hours before treating another episode of breakthrough pain with Fentora; in addition, they should limit their use of Fentora to four episodes per day.

Fentora is not bioequivalent to other fentanyl products, and the Health Canada product monograph warns against converting patients on a mcg-per-mcg basis from other fentanyl products. Patients switching from oral transmucosal fentanyl citrate (OTFC) may need a different starting dose of Fentora, as follows:

- Initial Fentora dose of 100 mcg if switching from OTFC dose of 200 or 400 mcg
- Initial Fentora dose of 200 mcg if switching from OTFC dose of 600 or 800 mcg
- Initial Fentora dose of 400 mcg if switching from OTFC dose of 1200 or 1600 mcg.

Indication under review
Management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant* to continuous opioid therapy for their persistent baseline cancer pain. *Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine daily or an equianalgesic dose of another opioid daily for a week or longer.
Reimbursement criteria requested by sponsor
Management of breakthrough pain in advanced cancer patients 18 years of age or older with the underlying pain adequately managed using a continuous opioid therapy (persistent baseline cancer pain) and one or more of: • Lack of adequate pain relief and/or intolerable opioid-related toxicities or adverse events or contraindication to any one of the following short acting / immediate release opioids: morphine, oxycodone, hydromorphone and/or • Difficulty to swallow (dysphagia)

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of Fentora (fentanyl buccal/sublingual effervescent tablets) 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.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Cancer patients aged 18 years of age and older with breakthrough pain who are already receiving and who are tolerant[a] to continuous opioid therapy for their persistent baseline cancer pain. Subgroup of interest: • Palliative care patients versus non-palliative care patients
Intervention	Fentora (fentanyl buccal/sublingual effervescent tablets) (100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg)[b]
Comparators	• Placebo (with permissible use of rescue medication to manage inadequate pain relief) • Short-acting opioids (at approved doses in Canada)
Outcomes	**Key efficacy outcomes:** • Change in pain intensity • Frequency of breakthrough pain episodes • Change in HRQoL • Use of rescue medications **Harms outcomes:** • Mortality • AEs • SAEs • WDAEs • Notable harms: dizziness, nausea, vomiting, constipation, somnolence, itchiness, respiratory depression, abuse, misuse, diversion
Study Design	Published and unpublished phase III RCTs

AE = adverse event; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine daily or an equianalgesic dose of another opioid daily for a week or longer.

[b] Per the Health Canada product monograph, Fentora is not bioequivalent with other fentanyl products. Further, patients must begin treatment using 100 mcg Fentora.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to

Present); Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Fentora (fentanyl citrate).

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on August 9, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on January 18, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Devices Regulatory Approvals, Advisories and Warnings, Drug Class Review, Databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and contacting appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

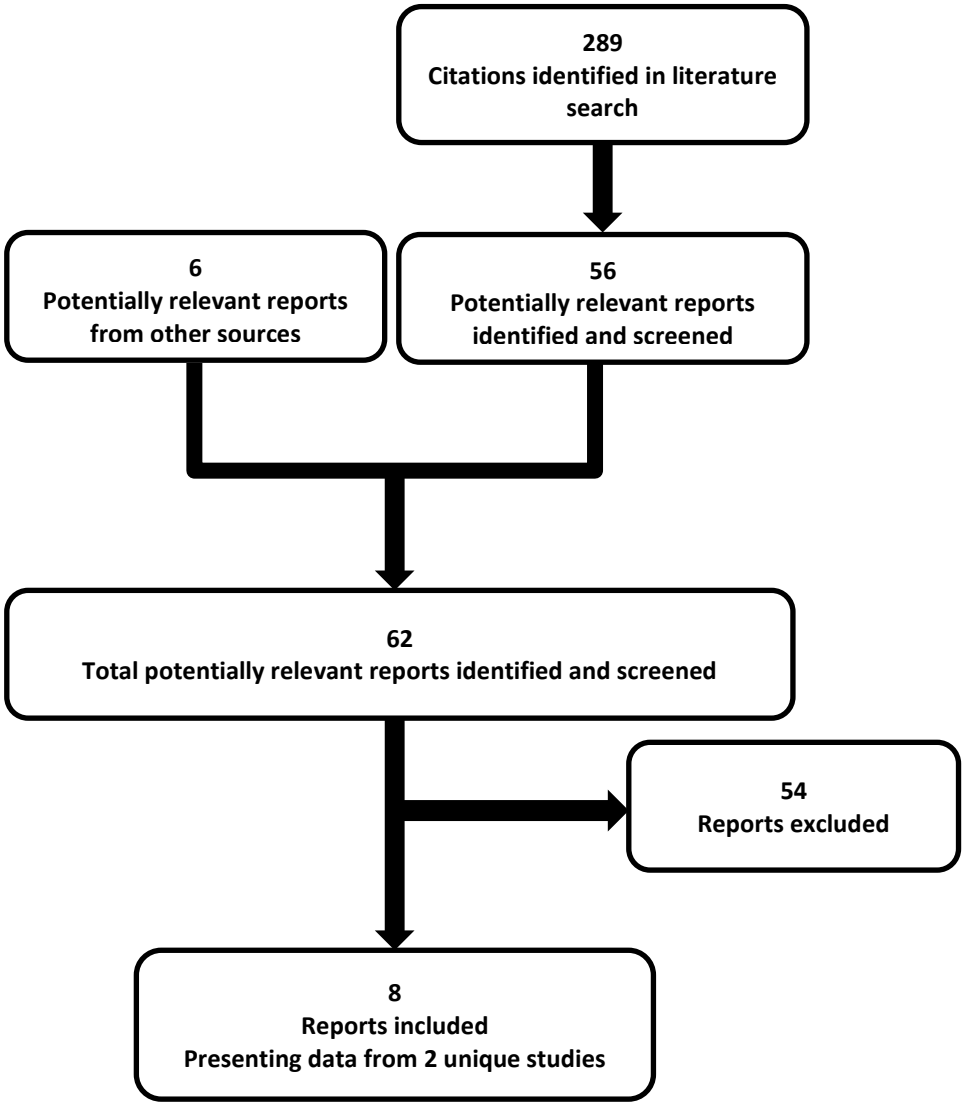


TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 14	Study 3039
Designs & Populations	**Study Design**	Multi-centre, DB, placebo-controlled phase III RCT	Multi-centre, DB, placebo-controlled phase III RCT stratified by successful dose of Fentora achieved during OL dose titration period
	Locations	US	US
	Randomized (N)	77	87
	Inclusion Criteria (Main)	Histologically documented diagnosis of a malignant solid tumour or a hematological malignancy causing cancer-related pain; experienced average of 1 to 4 episodes of breakthrough pain/day; if female and of childbearing potential: negative serum pregnancy test, was not lactating, and agreed to practice a reliable form of contraception or abstinence	
		Age ≥ 18 years; ECOG rating ≤ 2; life expectancy ≥ 3 months; used 60 mg to 1,000 mg of morphine/day or 50 mcg to 300 mcg/hour of transdermal fentanyl or opioid equivalent for ≥ 1 week for cancer-related pain	Age 18 to 80 years; life expectancy ≥ 2 months; used ≥ 60 mg/day of oral morphine or equivalent as ATC therapy, or used ≥ 25 mcg/hour of transdermal fentanyl for the previous 7 days; average 24-hour PI score < 7 (scale of 0 to 10)
	Exclusion Criteria (Main)	Sleep apnea or active brain metastases with increased intracranial pressure; recent history of substance abuse; neurologic or psychiatric impairment; recent therapy (within 30 days) that would alter pain or responses to analgesics	
		Use of intrathecal opioids; experiencing mucositis/stomatitis of grade ≥ 2 per CTCAE v3.0; COPD characterized by CO_2 retention; abnormal renal or hepatic function tests; at risk of significant bradyarrhythmia because of underlying heart disease; had primary source of breakthrough not cancer related	Uncontrolled or rapidly escalating pain; participated in a previous study with study drug; received MAOI within 14 days before treatment; presence of cardiopulmonary disease that could have increased the risk of treatment
Drugs	**Intervention**	Fentora (fentanyl buccal/sublingual effervescent tablets) (100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg) (titrated from 100 mcg)	
	Comparator(s)	Placebo	
	Phase		
	OL dose titration period	Up to 21 days	Approximately 7 days
	DB treatment period	Up to 21 days	
Outcomes	**Primary End Point**	SPID at 30 minutes	SPID at 60 minutes
	Other End Points	Efficacy: SPID at 15, 45, 60 minutes; PID at 15, 30, 45, 60 minutes; PR at 15, 30, 45, 60 minutes; TOTPAR at 15, 30, 45, 60 minutes; global medication performance assessment at 30 and 60 minutes; rescue medication use (rate and time to use)	Efficacy: SPID at 30, 90, 120 minutes; PID at 5, 10, 15, 30, 45, 60, 90, 120 minutes; PR at 5, 10, 15, 30, 45, 60, 90, 120 minutes; TOTPAR at 60, 90, 120 minutes; time to meaningful PR; global medication performance assessment at 60 and 120 minutes;

		Study 14	Study 3039
		Harms: AEs, SAEs, WDAEs, notable harms	rescue medication use; preference for breakthrough pain medication Harms: AEs, SAEs, WDAEs, notable harms
Notes	**Publications**	Portenoy et al., 2006[15]	Slatkin et al., 2007[16]

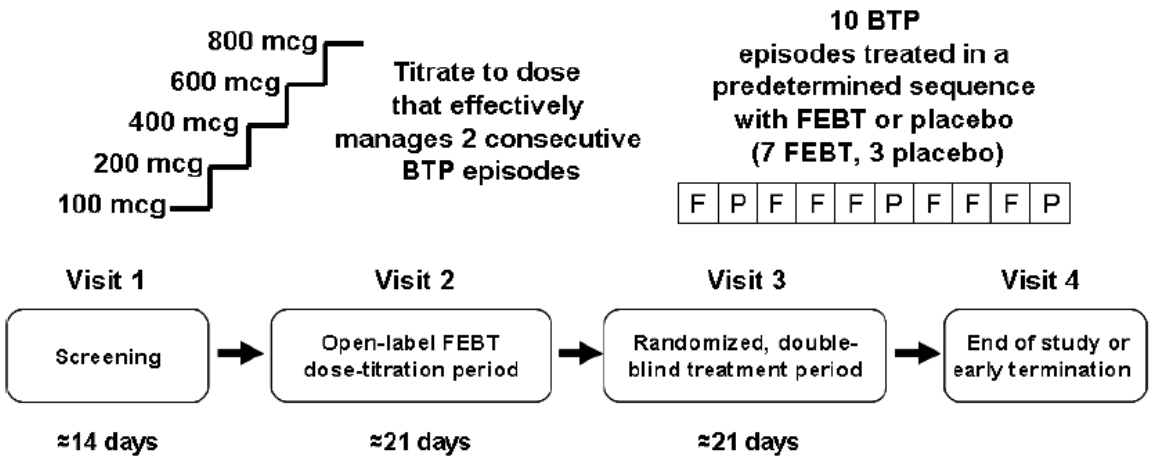
AE = adverse event; CDR = CADTH Common Drug Review; COPD = chronic obstructive pulmonary disease; CSR = Clinical Study Report; CTCAE = Common Terminology Criteria for Adverse Events; DB = double-blind; ECOG = Eastern Cooperative Oncology Group; FDA = Food and Drug Administration; MAOI = monoamine oxidase inhibitor; OL = open-label; PI = pain intensity; PID = pain intensity difference; PR = pain relief; RCT = randomized controlled trial; SAE = serious adverse event; SPID = summed pain intensity difference; TOTPAR = total pain relief; WDAE = withdrawal due to adverse event.
Note: The following additional reports were included: CDR submission,[17] FDA medical review,[18] FDA statistical review,[19] Health Canada reviewer's report.[20]
Source: Study 14 CSR;[21] Study 3039 CSR.[22]

3.2 Included Studies

3.2.1 Description of studies

Studies 14 (N = 77) and 3039 (N = 87) were similarly designed multi-centre, double-blind (DB), placebo-controlled, phase III randomized controlled trials (RCTs) conducted in the US. Each trial comprised a screening period, an open-label (OL) dose titration period, and a DB treatment period (Figure 2). The purpose of the titration period was to determine a successful dose for each participant. During the treatment period, patients received 10 tablets, of which seven were Fentora at the successful dose and three were placebo. Patients were then randomized to take these 10 tablets in one of 18 predetermined treatment sequences (Figure 2). They were allowed up to 21 days to complete the treatment period, after which they were invited to participate in an OL long-term safety study, the results of which are summarized in 0.

FIGURE 2: DESIGN OF STUDIES 14 AND 3039



BTP = breakthrough pain; FEBT = fentanyl effervescent buccal tablet.
Source: CADTH Common Drug Review submission.[17]

3.2.2 Populations

a) Inclusion and exclusion criteria

Studies 14 and 3039 enrolled opioid-tolerant men and women at least 18 years of age with a histologically documented diagnosis of a malignant solid tumour or a hematological malignancy causing cancer-related pain (Table 4). Patients were required to have a life expectancy of at least two months in Study 3039, and at least three months in Study 14. In each trial, eligible patients were those who were experiencing, on average, one to four episodes of breakthrough pain per day that were adequately controlled with a stable dose of standard rescue medication. Patients were also required to have been receiving at least 60 mg of oral morphine/day (up to 1,000 mg in Study 14; no upper limit in Study 3039), or 50 mcg to 300 mcg/hour (Study 14) or at least 25 mcg/hour (Study 3039) of transdermal fentanyl or an equivalent dose of opioid therapy for their cancer pain for at least one week prior to screening. Unlike in Study 3039, patients in Study 14 were required to have an Eastern Cooperative Oncology Group (ECOG) performance status rating no greater than two points. Patients in Study 3039 were required to have an average pain intensity (PI) score, over the prior 24 hours, of less than 7 on an 11-point scale (0 to 10), while there was no PI score requirement for Study 14. Further, there were no restrictions for intrathecal opioid use and mucositis in Study 3039.

b) Baseline characteristics

Patients appeared to be slightly older in Study 14 (mean age of 57.5 years of those who entered the DB treatment period) than in Study 3039 (mean age of 53.9 years) (Table 5). Further, 32% of patients in Study 14 were older than 65 years compared with 12% of patients in Study 3039.[17] The maximum age was 82 years in Study 14, compared with the maximum age of 75 years in Study 3039; of note, there was an age limitation of 80 years in Study 3039. Further, 62% of patients in Study 3039 were female, while fewer than half were female in Study 14. Patients in Study 14 had a lower median body mass index (26.0 kg/m^2) at baseline than those in Study 3039 (28.4 kg/m^2). Of patients who entered the DB treatment period, there were more white patients in Study 14 (88%) than in Study 3039 (79%). Of the overall populations in each study, a greater percentage of patients in Study 14 reported experiencing predominantly nociceptive pain (55%) than those in Study 3039 (41%), while approximately one in every five patients in each study reported the pain to be predominantly neuropathic.

Compared with patients in Study 14, patients in Study 3039 used higher mean daily doses of opioids used as ATC medication (279.2 mg/day in Study 3039 versus 213.5 mg/day in Study 14) as well as rescue medication (24.7 mg/day in Study 3039 versus 20.2 mg/day in Study 14) (Table 5). The reason for this discrepancy was unclear, although it should be noted that, in Study 14, ATC opioid use at baseline was required to be between 60 mg and 1,000 mg oral morphine/day. Despite this criterion, 13 patients (11%) reported doses below, and one participant (< 1%) reported a dose above this range; these were recorded as protocol violations. Across both studies, the most commonly used ATC opioids were oxycodone, fentanyl, and morphine; for rescue medications, these were oxycodone/acetaminophen, and hydrocodone/acetaminophen.

Overall, one of the clinical experts consulted by the CDR team noted that any observed inequities among and between trials were minor and unlikely to substantially affect treatment response.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	Study 14		Study 3039	
	Overall (N = 123)[a]	DB Treatment Period (N = 77)	Overall (N = 125)[a]	DB Treatment Period (N = 86)
Age, mean (SD) (years)	58.0 (12.6)	57.5 (13.6)	54.9 (10.9)	53.9 (11.3)
Females, n (%)	56 (46)	35 (45)	77 (62)	53 (62)
Weight, mean (SD) (kg)	74.7 (18.5)	75.5 (17.9)	77.6 (21.9)	78.2 (23.0)
Height, mean (SD) (cm)	169.7 (11.1)	170.1 (11.1)	166.7 (11.8)	167.1 (12.4)
Race, n (%)				
White	109 (89)	68 (88)	102 (92)	68 (79)
Black	2 (2)	1 (1)	10 (8)	7 (8)
Other	12 (10)	8 (10)	13 (10)	11 (13)
Pain pathophysiology, n (%)				
Predominantly neuropathic	23 (19)	16 (21)	21 (17)	NR
Predominantly nociceptive	68 (55)	36 (47)	51 (41)	NR
Mixed	32 (26)	25 (32)	53 (42)	NR
Opioid used as ATC medication — overall				
n (%)	116[b] (94)	NR	125 (100)	NR
Mean (SD) morphine equivalent (mg/d)	213.5 (461.9)		279.2 (362.3)	
Median (min, max)	120.0 (5.0, 4800.0)		180.0 (60.0, 3198.0)	NR
Opioid used as ATC medication — specific drugs, n (%)				
Fentanyl	35 (30)	NR	41 (33)	NR
Methadone	9 (8)		15 (12)	
Morphine	40 (34)		25 (20)	
Oxycodone	42 (36)		41 (33)	
Oxycodone/acetaminophen (Oxycocet)	NR		4 (3)	
Hydromorphone	NR		7 (6)	
Hydrocodone/acetaminophen (Vicodin)	8 (7)		6 (5)	
Codeine/aspirin/carisoprodol (Soma compound with codeine)	NR		1 (< 1)	
Other[c]	12 (10)		NR	
Opioid used as rescue medication — overall				
n (%)	104[b]	NR	125 (100)	NR
Mean (SD) morphine equivalent (mg/breakthrough pain episode)	20.2 (20.3)		24.7 (44.6)	
Median (min, max)	15.5 (1.0, 160.0)		16.0 (4.0, 480.0)	

Characteristic	Study 14		Study 3039	
	Overall (N = 123)[a]	DB Treatment Period (N = 77)	Overall (N = 125)[a]	DB Treatment Period (N = 86)
Opioid used as rescue medication — specific drugs, n (%)				
Hydrocodone	7 (7)	NR	3 (2)	NR
Hydromorphone	11 (11)		15 (12)	
Morphine	18 (17)		11 (9)	
Oxycodone	13 (13)		23 (18)	
Oxycodone/acetaminophen (Oxycocet)	25 (24)		31 (25)	
Hydrocodone/acetaminophen (Vicodin)	22 (21)		25 (20)	
Fentanyl citrate	NR		15 (12)	
Methadone	NR		1 (< 1)	
Codeine/acetaminophen (Panadeine CO)	NR		1 (< 1)	
Other[c]	8 (8)		0	

ATC = around-the-clock; CSR = Clinical Study Report; DB = double-blind; NR = not reported; SD = standard deviation.
Note: Patients may have reported more than one drug for ATC and rescue medications.
[a] Safety analysis set.
[b] In Study 14, there were 7 (3%) patients with no ATC medication and 19 (15%) patients with no rescue medication recorded at screening.
[c] Reported by < 5% of patients. Other ATC medications include codeine/acetaminophen, hydrocodone, hydromorphone, meperidine, meperidine/promethazine, oxycodone/acetaminophen, propoxyphene, and propoxyphene/acetaminophen. Other rescue medications include codeine/acetaminophen, fentanyl citrate, hydrocodone/ibuprofen, meperidine, methadone, and propoxyphene/acetaminophen.
Source: Study 14 CSR;[21] Study 3039 CSR.[22]

3.2.3 Interventions

In Studies 14 and 3039, the purpose of the OL dose titration period was to determine a successful dose for each participant. The starting dose of Fentora in Study 14 was 100 mcg for all patients. In Study 3039, however, the starting dose depended on the dose of the medication used by a participant to treat breakthrough pain immediately prior to study entry, as shown in Figure 3.

FIGURE 3: STARTING DOSE OF FENTORA IN STUDY 3039

BTP medication taken prior to study entry	ORAVESCENT fentanyl dose for starting titration (mcg)	ORAVESCENT fentanyl doses dispensed for titration (mcg)
Oral immediate-release opioids	100	100, 200, 400, 600, 800
Oral transmucosal fentanyl citrate doses of 200, 400, and 600 mcg	100	100, 200, 400, 600, 800
Oral transmucosal fentanyl citrate at doses of 800, 1200, or 1600 mcg:		
800 mcg	200	200, 400, 600, 800
1200 mcg	400	400, 600, 800
1600 mcg	600	600, 800

BTP = breakthrough pain.
Source: Study 3039 Clinical Study Report.[22]

In each study, patients were instructed on how to titrate to achieve a successful dose. They proceeded to the DB phase of the study when they identified a dose that provided sufficient pain relief within 30 minutes for two consecutive episodes of breakthrough pain without unacceptable adverse events (AEs). This successful dose was used throughout the DB period. Patients who were unable to tolerate the lowest dose of Fentora, unable to achieve a successful dose in the 100 mcg to 800 mcg dose range, or unable to achieve adequate pain relief without unacceptable AEs were not eligible to continue in the study.

During the treatment period, patients received 10 blinded study drug tablets, of which seven were Fentora tablets at the successful dose, and three were matching placebo tablets. Patients were then randomized to take these tablets in one of 18 computer-generated sequences. They were instructed to take one tablet for each breakthrough pain episode and to not take additional tablets within four hours following study drug administration. The treatment period ended after the study drug was used for 10 breakthrough pain episodes. Patients were allowed to treat a maximum of four episodes of breakthrough pain per day with the study drug. Patients were allowed to use their pre-study rescue medications to treat (1) any breakthrough pain episode in excess of four per day; (2) any episode that occurred less than four hours after use of standard rescue medication; and (3) any episode for which pain relief was inadequate at 30 minutes after administration of the study drug.

3.2.4 Outcomes

a) Efficacy

In Studies 14 and 3039, patients were asked to complete several assessments with each dose of study drug taken during the DB treatment period and record the information in a diary (paper in Study 14; electronic in Study 3039) provided to them. In contrast to Study 3039, in Study 14, the information was reviewed by study personnel during daily telephone contact. In each trial, patients were specifically asked to evaluate PI, pain relief (PR), global medication performance (GMP), and use of standard rescue medication, as listed below.

Pain intensity assessment
Patients used an 11-point linear numerical rating scale (0 = no pain; 10 = worst pain) to evaluate PI. They were asked to rate their pain immediately prior to the administration of the study drug and at pre-specified time points after the administration of the study drug — 15, 30, 45, and 60 minutes in Study 14; and 5, 10, 15, 30, 45, 60, 90, and 120 minutes in Study 3039.

Pain relief assessment
Patients used a 5-point Likert scale (0 = none; 1 = slight; 2 = moderate; 3 = a lot; 4 = complete) to evaluate PR. They were asked to rate their PR at the same pre-specified time points as above after study drug administration.

Global medication performance assessment
Patients used a 5-point categorical scale (0 = poor; 1 = fair; 2 = good; 3 = very good; and 4 = excellent) to evaluate the degree to which the study drug performed in controlling breakthrough pain. They were asked to evaluate GMP at pre-specified time points after study drug administration — 30 and 60 minutes in Study 14; and 60 and 120 minutes in Study 3039.

Use of rescue medication
Patients recorded any use of standard rescue medication for breakthrough pain episodes for which a study drug was used.

The **primary** efficacy outcome in both studies was the summed pain intensity difference (SPID) — the summed pain intensity difference (PID) at each specified interval after administration of the study drug for each episode of breakthrough pain. Of note, the time point at which the primary efficacy outcome was evaluated was different across the two studies — 30 minutes ($SPID_{30}$) for Study 14, and 60 minutes ($SPID_{60}$) for Study 3039. $SPID_{30}$ was calculated for each episode of breakthrough pain as the sum of PID at 15 and 30 minutes after administration of study drug, as follows: $SPID_{30} = PID_{15} + PID_{30}$, where PID was the PI score at each time point minus the PI score immediately before the administration of the study drug. $SPID_{60}$ was calculated for each episode of breakthrough pain as the sum of PID at all time points through 60 minutes after administration of the study drug, as follows: $SPID_{60} = (⅓ \times PID_{5}) + (⅓ \times PID_{10}) + (⅓ \times PID_{15}) + PID_{30} + PID_{45} + PID_{60}$. The manufacturer indicated that it was necessary to "time-weight" the PIDs in Study 3039 because of the irregular time interval between assessments.

The **secondary** efficacy outcomes in Studies 14 and 3039 are shown in Figure 4. Of note, total PR (TOTPAR) was calculated as the sum of PR scores at each assessment of PR until the pre-specified time point after study drug administration.

FIGURE 4: EFFICACY OUTCOMES IN STUDIES 14 AND 3039

Category	Study 14	Study 3039
Primary efficacy variable		
	$SPID_{30}$	$SPID_{60}$
Secondary efficacy variables		
SPID	15, 45, and 60 minutes after administration of study drug	30, 90, and 120 minutes after administration of study drug
PID value	15, 30, 45, and 60 minutes after administration of study drug	5, 10, 15, 30, 45, 60, 90, and 120 minutes after administration of study drug
PR score	15, 30, 45, and 60 minutes after administration of study drug	5, 10, 15, 30, 45, 60, 90, and 120 minutes after administration of study drug
TOTPAR value	15, 30, 45, and 60 minutes after administration of study drug	60, 90, and 120 minutes after administration of study drug
Global medication performance assessment	30 and 60 minutes after administration of study drug	60 and 120 minutes after administration of study drug
Medication preference	Not rated	Preference for FEBT or prior rescue medication and general rating of study drug

FEBT=fentanyl effervescent buccal tablets; BTP=breakthrough pain; SPID=sum of pain intensity differences; PID=pain intensity difference; PR=pain relief; TOTPAR=total pain relief.

Source: CADTH Common Drug Review submission.[17]

In Study 3039, the manufacturer also intended to evaluate time to meaningful PR; however, as patients did not use the timing procedure as intended, this outcome was unknown.

b) Harms

Studies 14 and 3039 also collected safety data, including the occurrence of mortality, AEs, serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and notable harms.

3.2.5 Statistical analysis

The sample sizes for Studies 14 and 3039 were based on a study that used a similar design but a different transmucosal fentanyl formulation, specifically OTFC.[23] In particular, in Study 14, approximately 63 patients were required to provide more than 95% power to detect a treatment difference of 1.4 (no rationale provided) between Fentora and placebo for the primary efficacy outcome, with a standard deviation (SD) of the within-participant difference not exceeding 3.0. Further, in Study 3039, 70 evaluable patients were required to provide 90% power to detect a treatment difference of 3.0 — assumed to be clinically relevant by the manufacturer, although no specific rationale provided — for the primary efficacy outcome; i.e., $SPID_{60}$, using a one-sample t-test, alpha of 5% (two-sided), and an SD of 7.58. Of note, in Study 3039, after assuming that 10% of randomized patients would not be evaluable, and 20% to 40% of patients would withdraw during the OL dose titration period, up to 140 patients were required for enrolment.

In Study 14, the primary efficacy outcome ($SPID_{30}$) was evaluated using a repeated measures analysis of variance (ANOVA) with treatment and centre as fixed effects and participant as a random effect. The effect of treatment by study centre was evaluated using a separate ANOVA with treatment, centre, participant, and treatment-by-centre as factors. Two sets of efficacy analyses were to be carried out, one of which was on the full analysis set (FAS) and the other on the evaluable analysis set; if, however, there was a difference of less than 10% in the number of patients in these two analysis sets, then the analyses were conducted using data from the FAS only. To address the fact that the study design did not

balance treatment effects against period effects, a permutation test was performed on the primary efficacy outcome to evaluate the extent to which the results were robust. In brief, patients' data were reassigned to the 18 treatment sequences randomly, using equal probabilities; the primary efficacy analysis was repeated using the newly assigned data; and the process was repeated 10,000 times. The fraction of the resulting *P* values that was lower than that found in the primary efficacy analysis was considered an estimate of the permutation *P* value, and statistical significance was declared if this value was ≤ 0.05. For the primary efficacy analysis, an additional confirmatory analysis was to be conducted if the number of patients in the evaluable analysis set was less than 90% the size of the FAS. Further, an exploratory sensitivity analysis was conducted in which the primary analysis was repeated without the results of treating the first breakthrough pain episodes. The final model for the primary efficacy analysis was also the model to evaluate the difference between Fentora and placebo for the other SPID variables and TOTPAR, while a one-sample Wilcoxon signed rank test was used for PID, PR, and GMP. If the analysis for the primary efficacy outcome detected a treatment-by-centre interaction, then the secondary analyses included a treatment-by-centre interaction term. All secondary efficacy analyses were conducted on the FAS only. Statistical testing for all efficacy outcomes was two-tailed using $\alpha = 0.05$, with no adjustments for multiplicity. No subgroup analyses were planned or conducted.

A similar statistical analysis plan was designed for Study 3039 as for Study 14, with some differences. First, the primary efficacy outcome ($SPID_{60}$) was evaluated using a slightly different ANOVA model, with treatment as a fixed effect and participant as a random effect. Given the small number of patients per centre, no analyses of treatment-by-centre interactions were conducted. As above, the FAS and the evaluable set were used for the efficacy analyses. As above, a permutation test was conducted to assess the robustness of the primary efficacy results. The model for the primary efficacy analysis was also the model for the secondary variables of SPID, PID, and TOTPAR. A one-sample Wilcoxon signed rank test was used to evaluate PR. All statistical testing was two-tailed using $\alpha = 0.05$, with no adjustments for multiplicity. Exploratory analyses for the secondary variables SPID, PID, PR, and TOTPAR were conducted based on the randomized treatment and not the actual treatment. No subgroup analyses were planned or conducted.

a) Analysis populations

Across Studies 14 and 3039, the safety analysis set included enrolled patients who received at least one dose of the study drug during the dose titration period. The DB safety analysis included patients in the safety analysis set who received at least one dose of the study drug during the DB treatment period; further, in Study 14, this group was referred to as the intention-to-treat (ITT) analysis set. In both studies, the FAS included patients in the DB safety analysis set who took Fentora for at least one episode of breakthrough pain and took placebo for at least one episode of breakthrough pain during the DB treatment period; in Study 14, patients contributing to this set had to also have at least one pre-treatment PI score and one post-treatment PI score for each of these episodes, while in Study 3039, they only needed to have one pre-treatment PI score for each of these episodes. Further, in Study 14, this group was referred to as the modified intention-to-treat (mITT) analysis set. In both studies, the evaluable analysis set included evaluable patients in the FAS who took Fentora for at least one evaluable episode of breakthrough pain and took placebo for at least one evaluable episode of breakthrough pain during the DB treatment period. Of note, evaluable patients did not have any inclusion or exclusion criteria violations, and did not have other major violations, while evaluable episodes of breakthrough pain were those that had PI scores at baseline, and both 15 and 30 minutes later.

3.3 Participant Disposition

In Study 14, 123 patients with breakthrough pain secondary to cancer were enrolled and received at least one dose of the study drug (Table 6). Of these patients, 77 (62.6%) completed the dose titration period and were randomized to DB treatment and 68 (55.3%) completed the treatment period. Twenty (16.3%) patients did not achieve a successful dose during the dose titration period due to lack of efficacy and were not eligible to enter the DB treatment period, whereas no participant withdrew from the study due to lack of efficacy during the DB treatment period. In Study 3039, of 129 patients with breakthrough pain secondary to cancer who were enrolled and received at least one dose of study drug, four individuals were not treated (Table 6). Thirty-eight (29.5%) individuals withdrew during the titration period, most commonly due to occurrence of AE, leaving 87 patients who entered the DB treatment period. Twelve individuals withdrew during the DB treatment period, leaving 75 patients who completed treatment. In general, participant disposition between the studies was similar. Of note, however, in Study 14, a greater percentage of patients (16.3%) withdrew due to lack of efficacy during the dose titration period than in Study 3039 (6.2%).

TABLE 6: PARTICIPANT DISPOSITION

	Study 14	Study 3039
Screened, N	139	175
Enrolled, N	123	129
Not treated, n (%)	0	4 (3.1)
Withdrew during OL dose titration period, N (%)	46 (37.4)	38 (29.5)
Lack of efficacy, n (%)	20 (16.3)	8 (6.2)
AE, n (%)	12 (9.8)	14 (10.9)
Consent withdrawn, n (%)	6 (4.9)	8 (6.2)
Protocol violation, n (%)	0	1 (0.7)
Lost to follow-up, n (%)	1 (0.8)	0
Non-compliance to study drug administration, n (%)	NA	1 (0.8)
Non-compliance to study drug procedures, n (%)	NA	2 (1.6)
Other, n (%)	7 (5.7)	4 (3.1)
Achieved successful dose during titration period, N	80 (65.0)	87 (67.4)
Entered DB treatment period, N	77[a] (62.6)	87 (67.4)
Not treated, n (%)	0	1 (0.8)
Withdrew during DB treatment period, N	9 (7.3)	12 (9.3)
AE, n (%)	3 (2.4)	5 (3.9)
Consent withdrawn, n (%)	4 (3.3)	3 (2.3)
Lost to follow-up, n (%)	0	1 (0.8)
Other, n (%)	2 (1.6)	3 (2.3)
Completed DB treatment period, N	68 (55.3)	75 (58.1)
Full analysis set, N	72 (58.5)	78 (60.5)
Evaluable analysis set, N	70 (56.9)	70 (54.3)
Safety analysis set, N	123 (100)	125 (96.9)
DB safety analysis set, N	77 (62.6)	86 (66.7)

AE = adverse event; CSR = Clinical Study Report; DB = double-blind; NA = not applicable; OL = open-label.
a Three patients achieved a successful dose during the titration period, but did not enter the treatment period.
Source: Study 14 CSR,[21] Study 3039 CSR.[22]

3.4 Exposure to Study Treatments

Across both studies, of the patients who entered the DB treatment period, the most commonly identified successful dose was the highest dose of Fentora; i.e., 800 mcg — specifically, 31% and 35% of patients in Studies 14 and 3039, respectively, were administered that dose (Table 7). In Study 3039, the manufacturer reported that while there was "no clear relationship" between the successful dose of Fentora and the dose of transdermal fentanyl ATC medication taken during the study, it appeared as if individuals who were taking higher doses of non-transdermal fentanyl ATC medication tended to be using higher successful doses of Fentora during the study.[22] This trend is generally consistent with the expectations of one of the consulting clinical experts, who indicated that patients who were receiving higher ATC opioid doses would require higher doses of Fentora to achieve adequate pain relief, although it was unclear why there was an apparent difference with the type of ATC medication; i.e., transdermal fentanyl versus non-transdermal fentanyl. These trends did not appear to be explored in Study 14. The mean (SD) duration of exposure to the study drug in Study 3039 (not reported in Study 14) was 8.8 (6.23) days.

TABLE 7: STUDY DRUG ADMINISTRATION DURING TREATMENT PERIOD

	Study 14 (N = 77)	Study 3039 (N = 86)
Successful dose of Fentora, n (%)		
100 mcg	12 (16)	6 (7)
200 mcg	11 (14)	10 (12)
400 mcg	20 (26)	16 (19)
600 mcg	10 (13)	24 (28)
800 mcg	24 (31)	30 (35)
Duration of exposure, mean (SD) days	NR	8.8 (6.23)
Duration of exposure, median (range) days		7.0 (1, 40)

SD = standard deviation.
Note: Safety analysis set.

In Study 14, the overall mean compliance was 92.3%, and it appeared that patients who were receiving 100 mcg of Fentora were less compliant (80.0%) than the rest of the patients (range of 89.5% to 99.0%), although it was unclear why this may have been the case (Table 8). Of note, however, the median compliance overall and across all groups was 100%. There was no information about study drug compliance in Study 3039.

TABLE 8: STUDY DRUG COMPLIANCE DURING TREATMENT PERIOD

	Study 14	Study 3039
Compliance,[a] mean % (SD)		
100 mcg	80.0 (36.4)	NR
200 mcg	92.7 (15.6)	
400 mcg	89.5 (28.0)	
600 mcg	99.0 (3.2)	
800 mcg	97.9 (10.2)	
Overall	92.3 (22.2)	

CSR = Clinical Study Report; NR = not reported; SD = standard deviation.
[a] Defined as the percentage of tablets of study drug used relative to the expected number (10).
Source: Study 14 CSR;[21] Study 3039 CSR.[22]

3.5 Critical Appraisal

3.5.1 Internal validity

In Studies 14 and 3039, during the DB treatment period, patients were randomized to take 10 tablets, of which seven were Fentora at the successful dose and three were placebo. As the manufacturer acknowledges, there were a possible 120 sequences in which the patients could have taken the 10 tablets. However, several constraints were placed on the sequences — i.e., a placebo tablet could not be used for the first breakthrough pain episode; a placebo tablet could not be used for adjacent episodes; one placebo tablet was used for episode 2 or 3; one placebo tablet was used for episode 4, 5, or 6; and one placebo tablet was used for episode 7, 8, 9, or 10 — which limited the number of eligible sequences to 18. As a result, the order in which the patients received the treatments was not "completely random," as noted by the FDA.[19] The manufacturer, in response to the FDA, conducted a permutation test that confirmed the results of the primary efficacy outcome (i.e., $SPID_{30}$ in Study 14, and $SPID_{60}$ in Study 3039); of note, no such tests were conducted for the other outcomes, which leaves uncertain the degree to which the results for these outcomes were robust. Further, no details were provided about the allocation concealment processes in the two studies, which raises the possibility of selection bias and may reduce the validity of the results.

Both studies were described as DB, and the manufacturer confirmed that the placebo tablets looked and tasted identical to the Fentora tablets, and both sets of tablets featured the same effervescence associated with their disintegration and dissolution.

Both trials evaluated the effects of Fentora versus placebo across a number of efficacy and safety outcomes. The results of all outcomes other than the primary efficacy outcome should be considered as exploratory and be interpreted with caution, as they were not adjusted for multiplicity, which increases the risk of making a type I error.

Neither of the two studies used a true ITT population, as they did not analyze data from all randomized patients. Missing data were imputed using the last observation carried forward (LOCF) method, whereby baseline values were carried forward into the treatment period. Carrying the last observation forward may, however, artificially stabilize pain intensity levels among patients who dropped out; conversely, observed data could also be biased if the probability of withdrawal is related to an increase in pain intensity levels. The manner in which the studies were designed makes it challenging to hypothesize the direction in which the treatment effects may have been biased, as patients may have withdrawn at different times during the treatment period. In other words, some individuals may have withdrawn after taking their first study drug, which was always Fentora, while others may have withdrawn later in their respective treatment sequences.

In both studies, patients were, in essence, crossing over between Fentora and placebo multiple times. While the manufacturer conducted an exploratory sensitivity analysis in which the primary analysis was repeated without the results of treating the first breakthrough pain episodes, this is not the same as testing for carry-over (residual) effects, which is a concern in within-participant trial designs such as Studies 14 and 3039. To this end, to corroborate the results, the FDA statistical reviewer reanalyzed the primary efficacy outcome from Study 14 (Study 3039 was not submitted for regulatory approval in the US) using an ANOVA model that included sequence and period terms in addition to treatment, study site, and participant terms. Still, not testing (and accounting) for the carry-over effects in Study 3039 necessitates additional caution in interpreting the observed effects from that trial.

Another threat to the internal validity of both studies is that the manner in which patients may have perceived their pain might have changed over the course of the trials. Pain is a subjective phenomenon, and the analysis did not account for intra-observer variability in pain intensity during the treatment period. This is particularly concerning for the outcome of SPID, because it statistically combines pain intensity measurements at different time points as if they were independent observations. This limitation further reduces the validity of the results of the SPID.

3.5.2 External validity

Discussions with one of the clinical experts consulted by CDR for this review highlighted that the generalizability of the findings of the two trials is a concern. Chiefly, given the numerous exclusion criteria, the studies appear to have enrolled a highly selective population. For instance, the same expert emphasized that it would be unlikely to find a patient in a typical pain management practice in Canada who would not be experiencing neurologic or psychiatric impairments. The expert also indicated that it would be unlikely if patients in a typical clinical setting would be screened for sleep apnea or substance abuse history, both of which were exclusion criteria across the included studies. In addition, a substantial percentage of patients (37.4% in Study 14; 29.5% in Study 3039) withdrew from the studies during the OL dose titration period, which further restricts the clinical population to which the results of the studies may be directly applied.

Of note, there is an apparent disconnect between the requested reimbursement criteria and the trial populations. For instance, there was no requirement for the trial patients to have dysphagia or a contraindication to other short-acting/IR opioids, both of which were included as possible limiters in the requested reimbursement criteria. The expert indicated that the Fentora tablet (given the manner in which it disintegrates) is particularly attractive to patients with dysphagia, since approximately half of it is absorbed transmucosally.

Given the cancer setting, the same clinical expert expected that patients would be receiving ATC opioids at higher doses than patients with non-cancer pain. While the expert indicated that the equivalent of 200 mg/day of morphine is considered to be the “watchful dose” for patients with chronic non-cancer pain, to the expert’s knowledge, there is not an analogous dose for those with cancer-related pain. The expert was, however, reassured to see that the mean daily dose of opioids used as rescue medication was roughly 10% of the ATC medication dose, which is what the expert would have expected. Across both studies, the most commonly used ATC opioids were oxycodone, fentanyl, and morphine. The expert indicated that oxycodone would be prescribed much less frequently in typical clinical practice in Canada; instead, hydromorphone and morphine would be more commonly prescribed.

Both studies evaluated the efficacy and safety of the study treatments across a range of outcomes. The primary efficacy outcome in both trials was the SPID, which the expert mentioned is not an outcome used to evaluate treatment response in routine clinical practice. Further, the absence of a patient input submission for this review leaves uncertain unevaluated outcomes that may be important to patients. Nevertheless, the clinical expert indicated that it would be important to examine the effects of the study treatments on health-related quality of life (HRQoL), which was not done in either trial. Further, the manner in which both studies were designed precluded an assessment of the relative safety of Fentora. Last, neither of the trials captured some important safety outcomes that are associated with short-acting opioids, including abuse, misuse, and diversion; even if they had, however, the durations of the studies were insufficient to adequately assess the long-term safety profile of Fentora.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (Section 2.2, Table 3) are reported below.

3.6.1 Change in pain intensity

a) Summed pain intensity difference

In Study 14, Fentora was associated with a statistically significant reduction in mean SPID compared with placebo at 15, 30, 45, and 60 minutes after study drug administration (Table 9). In Study 3039, Fentora was associated with a statistically significant reduction in mean SPID compared with placebo at 30, 60, 90, and 120 minutes after study drug administration.

TABLE 9: RESULTS OF SUMMED PAIN INTENSITY DIFFERENCE

	Study 14		Study 3039	
	Fentora (n = 72)	Placebo (n = 72)	Fentora (n = 78)	Placebo (n = 78)
Reduction at 15 minutes				
LSM (SE)	0.8 (0.06)	0.5 (0.08)	Not evaluated	
Difference (95% CI), *P* value[a]	**0.3[b] (NR), *P* < 0.0001**			
Reduction at 30 minutes (primary outcome in Study 14)				
LSM (SE)	3.0 (0.12)	1.8 (0.18)	3.3 (0.1)	1.9 (0.2)
Difference (95% CI), *P* value[a]	**1.2[b] (0.8 to 1.6), *P* = 0.0005**		**1.4[b] (1.1 to 1.8), *P* < 0.0001**	
Reduction at 45 minutes				
LSM (SE)	6.3 (0.2)	3.6 (0.3)	Not evaluated	
Difference (95% CI), *P* value[a]	**2.7[b] (NR), *P* < 0.0001**			
Reduction at 60 minutes (primary outcome in Study 3039)				
LSM (SE)	10.2 (0.3)	5.8 (0.4)	9.8 (0.3)	5.0 (0.4)
Difference (95% CI), *P* value[a]	**4.4[b] (NR), *P* < 0.0001**		**4.8 (3.9 to 5.6), *P* < 0.0001**	
Reduction at 90 minutes				
LSM (SE)	Not evaluated		17.0 (0.4)	8.5 (0.6)
Difference (95% CI), *P* value[a]			**8.5[b] (7.0 to 9.9) to *P* < 0.0001**	
Reduction at 120 minutes				
LSM (SE)	Not evaluated		24.3 (0.6)	12.1 (0.9)
Difference (95% CI), *P* value[a]			**12.2[b] (10.2 to 14.2), *P* < 0.0001**	

ANOVA = analysis of variance; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; CI = confidence interval; LSM = least squares mean; NR = not reported; SE = standard error.

[a] In Study 14, the LSM, SE of LSM, and *P* value were based on a repeated measures ANOVA with treatment, centre, and participant within centre as factors. In Study 3039, the *P* value was based on an ANOVA with treatment as a fixed factor and participant as a random factor.

[b] Calculated by the CDR clinical review team as difference between Fentora and placebo.

Source: Study 14 CSR;[21] Study 3039 CSR.[22]

b) Pain intensity difference

In Study 14, Fentora was associated with a statistically significant reduction in mean PID compared with placebo at 15, 30, 45, and 60 minutes after study drug administration (Table 10, Figure 5, Figure 6). In Study 3039, Fentora was associated with a statistically significant reduction in mean PID at 10, 15, 30, 45, 60, 90, and 120 minutes after study drug administration (Figure 6).

TABLE 10: RESULTS OF PAIN INTENSITY DIFFERENCE

	Study 14		Study 3039	
	Fentora (n = 72)	Placebo (n = 72)	Fentora (n = 78)	Placebo (n = 78)
Baseline				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	6.9 (1.6)	6.9 (1.6)	6.4 (0.04)	6.4 (0.05)
Difference (95% CI), *P* value[a]	0.0[b] (NR), *P* = 0.7319		0.0[b] (–0.15 to 0.10), *P* = 0.7133	
Reduction at 5 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	Not evaluated		0.3 (0.03)	0.3 (0.04)
Difference (95% CI), *P* value[a]			0.0[b] (–0.06 to 0.14), *P* = 0.4125	
Reduction at 10 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	Not evaluated		0.9 (0.04)	0.5 (0.06)
Difference (95% CI), *P* value[a]			**0.[4b] (0.20 to 0.48), *P* < 0.0001**	
Reduction at 15 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	0.9 (1.1)	0.6 (0.9)	1.5 (0.06)	0.8 (0.09)
Difference (95% CI), *P* value[a]	**0.3[b] (NR), *P* = 0.0029**		**0.7[b] (0.45 to 0.85), *P* < 0.0001**	
Reduction at 30 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	2.3 (1.5)	1.4 (1.4)	2.4 (0.08)	1.3 (0.11)
Difference (95% CI), *P* value[a]	**0.9[b] (NR), *P* < 0.0001**		**1.1[b] (0.83 to 1.35), *P* < 0.0001**	
Reduction at 45 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	3.3 (1.8)	1.9 (1.6)	3.1 (0.08)	1.5 (0.12)
Difference (95% CI), *P* value[a]	**1.4[b] (NR), *P* < 0.0001**		**1.6[b] (1.30 to 1.86), *P* < 0.0001**	
Reduction at 60 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	4.0 (2.0)	2.3 (1.9)	3.4 (0.09)	1.7 (0.13)
Difference (95% CI), *P* value[a]	**1.7[b] (NR), *P* < 0.0001**		**1.7[b] (1.45 to 2.04), *P* < 0.0001**	
Reduction at 90 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	Not evaluated		3.6 (0.09)	1.7 (0.13)
Difference (95% CI), *P* value[a]			**1.9[b] (1.56 to 2.16), *P* < 0.0001**	
Reduction at 120 minutes				
Mean (SD) [Study 14] / LSM (SE) [Study 3039]	Not evaluated		3.7 (0.09)	1.8 (0.13)
Difference (95% CI), *P* value[a]			**1.9[b] (1.55 to 2.16), *P* < 0.0001**	

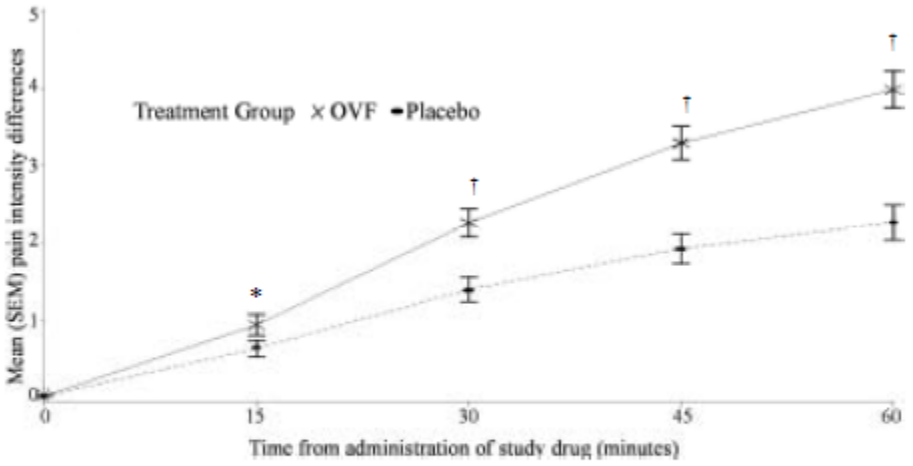
ANOVA = analysis of variance; CDR = CADTH Common Drug Review; CI = confidence interval; CSR = Clinical Study Report; LSM = least squares mean; NR = not reported; SD = standard deviation; SE = standard error.

[a] In Study 14, the *P* value was based on a one-sample Wilcoxon signed rank test. In Study 3039, the *P* value was based on an ANOVA with treatment as a fixed factor and participant as a random factor.

[b] Calculated by the CDR clinical review team as difference between Fentora and placebo.

Source: CDR submission,[17] Study 14 CSR,[21] Study 3039 CSR.[22]

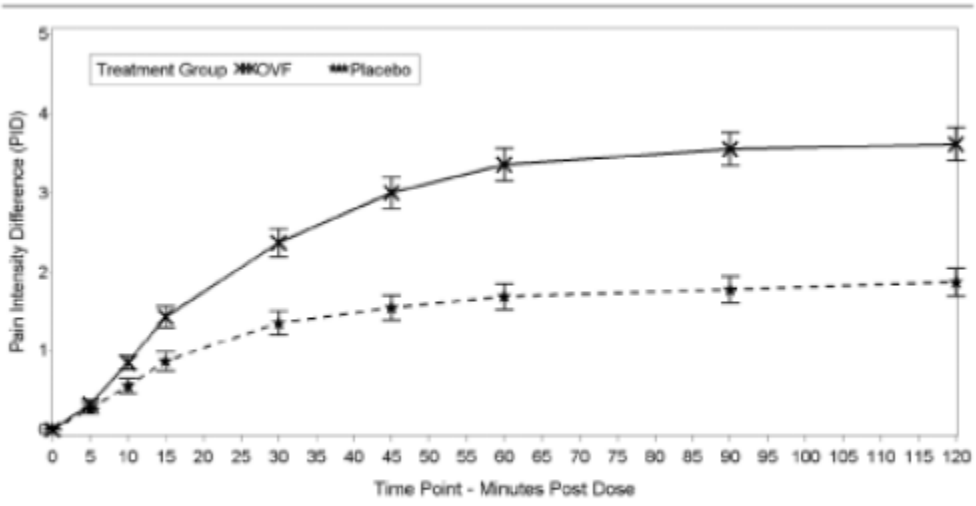
FIGURE 5: MEAN PAIN INTENSITY DIFFERENCE AT EACH TIME POINT DURING THE DOUBLE-BLIND TREATMENT PERIOD IN STUDY 14



SOURCE: Summary 15.14, Listing 12.
*p<0.01 OVF versus placebo, in favor of OVF, by one-sample Wilcoxon signed rank test
†p<0.0001 OVF versus placebo, in favor of OVF, by one-sample Wilcoxon signed rank test
PID=pain intensity difference; OVF=ORAVESCENT fentanyl; SEM=standard error of the mean.

Source: Study 14 Clinical Study Report.[21]

FIGURE 6: MEAN PAIN INTENSITY DIFFERENCE AT EACH TIME POINT DURING THE DOUBLE-BLIND TREATMENT PERIOD IN STUDY 3039



SOURCE: Section 15, Figure 1.
SEM=standard error of the mean; OVF= ORAVESCENT fentanyl.

Source: Study 3039 Clinical Study Report.[22]

In Study 14, at 15, 30, 45, and 60 minutes after study drug administration, a statistically greater percentage of breakthrough pain episodes treated with Fentora were characterized by ≥ 33% improvement in pain intensity than those who were treated with placebo (Table 11). The difference in

the percentage of episodes with an improvement in pain intensity of ≥ 50% was also statistically significant in favour of Fentora from 30 minutes onward. In Study 3039, at 10, 15, 30, 45, 60, 90, and 120 minutes after study drug administration, a statistically greater percentage of breakthrough pain episodes treated with Fentora were characterized by ≥ 33% and ≥ 50% improvements in pain intensity versus placebo (Table 12).

TABLE 11: NUMBER (%) OF EPISODES WITH ≥ 33% AND ≥ 50% IMPROVEMENT IN PAIN INTENSITY IN STUDY 14

Time Point	Improvement in Pain Intensity					
	≥ 33%			≥ 50%		
	Fentora	Placebo	*P* value	Fentora	Placebo	*P* value
15 minutes	69 (13)	20 (9)	< 0.05	44 (8)	13 (6)	NS
30 minutes	240 (48)	61 (29)	< 0.0001	122 (24)	34 (16)	< 0.05
45 minutes	352 (71)	93 (44)	< 0.0001	253 (51)	52 (25)	< 0.0001
60 minutes	373 (75)	100 (48)	< 0.0001	319 (64)	74 (35)	< 0.0001

Source: Portenoy et al., 2006.[15]

TABLE 12: NUMBER (%) OF EPISODES WITH ≥ 33% AND ≥ 50% IMPROVEMENT IN PAIN INTENSITY IN STUDY 3039

Time Point	Improvement in Pain Intensity					
	≥ 33%			≥ 50%		
	Fentora	Placebo	*P* value[a]	Fentora	Placebo	*P* value
5 minutes	23 (5)	6 (3)	0.120	9 (2)	4 (2)	0.9436
10 minutes	77 (16)	23 (10)	0.0072	34 (7)	9 (4)	0.0332
15 minutes	145 (29)	32 (14)	< 0.0001	89 (18)	18 (8)	< 0.0001
30 minutes	253 (51)	58 (26)	< 0.0001	186 (38)	34 (15)	< 0.0001
45 minutes	319 (65)	70 (31)	< 0.0001	259 (53)	44 (20)	< 0.0001
60 minutes	342 (69)	73 (33)	< 0.0001	292 (59)	50 (22)	< 0.0001
90 minutes	360 (73)	80 (36)	< 0.0001	313 (63)	58 (26)	< 0.0001
120 minutes	363 (74)	85 (38)	< 0.0001	324 (66)	62 (28)	< 0.0001

[a] Based on a Generalized Estimating Equation model with a logit link function adjusted for intrapatient correlation.
Source: Study 3039 Clinical Study Report.[22]

3.6.2 Frequency of breakthrough pain episodes

Neither of the trials evaluated the effects of the study treatments on the frequency of breakthrough pain episodes as an efficacy outcome.

3.6.3 Change in health-related quality of life

Neither of the trials evaluated the effects of the study treatments on HRQoL as an efficacy outcome.

3.6.4 Use of rescue medications

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).[17] 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).[17]

3.7 Harms

Only those harms identified in the review protocol (see Section 2.2, Table 3) are reported below.

3.7.1 Adverse events

Across Studies 14 and 3039, during the OL dose titration period and the DB treatment period, as well as overall, a numerically greater percentage of patients in Study 14 experienced a treatment-emergent adverse event (TEAE) than in Study 3039 — 66% versus 47% in the titration period; 61% versus 55% in the treatment period; and 77% versus 66% overall (Table 13). The reason for these discrepancies was unclear.

3.7.2 Serious adverse events

The rates of SAEs across the two studies were approximately equal. In particular, in Study 14, overall, 14 patients (11%) experienced an SAE; 12 patients (10%) experienced an SAE during the OL dose titration period; and four patients (5%) experienced an SAE during the DB treatment period (Table 13). The most frequently reported SAEs were asthenia, dehydration, cancer pain, and malignant lung neoplasm and, per the manufacturer, these were determined to be related to the patients' underlying conditions. In Study 3039, overall, 11 (9%) patients experienced an SAE; seven (6%) of the individuals were in the OL dose titration period; and four (5%) were in the DB treatment period. All of the SAEs were considered not related or unlikely to be related to treatment with the study drug.

3.7.3 Withdrawals due to adverse events

The rates of withdrawals due to AEs across the two studies were approximately equal (Table 13). In particular, 15 patients (12%) from Study 14 discontinued due to an AE, of whom three (4%) discontinued during the DB treatment period. In Study 3039, 19 patients (15%) discontinued due to an AE, of whom five (6%) discontinued during the DB treatment period.

3.7.4 Mortality

In Study 14, seven patients (6%) who withdrew from the study (two during the DB treatment period) subsequently died (Table 13). The deaths were considered not related or unlikely to be related to study drug treatment, and all deaths were attributable to disease progression. In Study 3039, eight patients (6%) who took the study drug died. Six patients died due to SAEs that, per the manufacturer, were progressions of their underlying diseases. All deaths were due to the patients' underlying conditions and were considered not related or unlikely to be related to the study drug.

3.7.5 Notable harms

Of most notable harms that were reported, specifically dizziness, nausea, vomiting, and somnolence, a numerically greater percentage of patients in Study 14 were affected than those in Study 3039 — 22% versus 11% for dizziness; 22% versus 13% for nausea; 11% versus 6% for vomiting; and 10% versus 0% for somnolence (Table 13). The occurrence of constipation was approximately equal (8% versus 6%) across the two studies. As with the differential rates of AEs across the two studies, the reason for the discrepancies in the occurrence of notable harms was unclear. There were no reported cases of respiratory depression in either study. Neither of the studies reported on abuse, misuse, or diversion.

TABLE 13: HARMS

	Study 14[a]			Study 3039[a]		
	OL Titration Period (N = 123)	DB Treatment Period (N = 77)	Overall (N = 123)	OL Titration Period (N = 125)	DB Treatment Period (N = 86)	Overall (N = 125)
Patients with > 0 TEAEs, n (%)	81 (66)	47 (61)	95 (77)	59 (47)	47 (55)	83 (66)
Patients with > 0 SAEs, n (%)	12 (10)	4 (5)	14 (11)	7 (6)	4 (5)	11 (9)
Withdrawals due to AEs, n (%)	12 (10)	3 (4)	15 (12)	14 (11)	5 (6)	19 (15)
Number of deaths, n (%)	5 (4)	2 (3)	7 (6)	3 (2)	3 (3)	8 (6)
Notable harms						
Dizziness, n (%)	25 (20)	6 (8)	27 (22)	10 (8)	4 (5)	14 (11)
Nausea n (%)	18 (15)	13 (17)	27 (22)	14 (11)	4 (5)	15 (13)
Vomiting n (%)	8 (7)	5 (6)	13 (11)	7 (6)	3 (3)	8 (6)
Constipation n (%)	8 (7)	2 (3)	10 (8)	4 (3)	3 (3)	7 (6)
Somnolence, n (%)	7 (6)	5 (6)	12 (10)	0		
Pruritus, n (%)	4 (3)	1 (1)	NR	1 (< 1)	1 (1)	NR
Pruritus generalized, n (%)	NR			1 (< 1)	NR	
Respiratory depression n (%)	0					
Abuse, n (%)	NR					
Misuse, n (%)						
Diversion, n (%)						

AE = adverse event; CSR = Clinical Study Report; DB = double-blind; NR = not reported; OL = open-label; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Safety analysis set.

Source: Study 14 CSR;[21] Study 3039 CSR.[22]

4. DISCUSSION

4.1 Summary of Available Evidence

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 OL dose titration period, and a DB treatment period. During the treatment period, patients received 10 study drug tablets — seven were Fentora, and three were placebo — in one of 18 random sequences. The primary efficacy outcome in both studies was SPID at 30 minutes for Study 14 and SPID at 60 minutes for Study 3039. Relevant secondary efficacy outcomes included PID and use of rescue medications, while relevant harms outcomes included mortality, AEs, SAEs, WDAEs, and several notable harms.

Both studies enrolled opioid-tolerant adults with cancer-related pain. Discussions with one of the clinical experts consulted by CDR for this review highlighted that the generalizability of the findings of the two trials is a concern. Chiefly, the numerous exclusion criteria and the substantial percentage of patients who withdrew from the studies during the OL dose titration period restrict the clinical population to which the results of the studies may be directly applied. Further, several methodological limitations necessitate caution in interpreting the observed results, including uncertainty with respect to the allocation concealment procedure, possible unblinding of study treatments, lack of adjustment for multiplicity for all secondary efficacy outcomes, limited exploration of the sensitivity of the results to the restricted randomization procedures, and lack of testing for carry-over effects.

4.2 Interpretation of Results

4.2.1 Efficacy

Results from Studies 14 and 3039 indicated that, compared with placebo, Fentora was associated with statistically significant reductions in mean SPID and PID as early as 10 minutes (PID) or 15 minutes (SPID) after study drug administration through to 120 minutes later (both outcomes). Of note, discussions with one of the consulting clinical experts indicated that SPID is not an outcome used to evaluate treatment response in routine clinical practice, which is why the ensuing discussion will focus on the PID. In addition, neither trial evaluated 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. Further, neither trial evaluated treatment effects specifically among patients with dysphagia or those who had lack of pain relief and/or intolerable opioid-related toxicities or AEs or contraindication to other IR opioids, both of which were included in the reimbursement request.

While Fentora consistently demonstrated statistically significant improvements in PID versus placebo, it is important to understand the degree to which these results are clinically meaningful. A decrease of ≥ 2 points on a numeric rating scale for PID is generally considered to reflect a clinically meaningful reduction in pain intensity.[24,25] However, this difference refers usually to the change in PID observed within a treatment group, and not the between-group difference; the latter is more meaningful, since it relates to the *relative* efficacy of a treatment rather than its *absolute* efficacy. 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. Discussions with one of the consulting experts suggested that a clinically important between-group difference might be expected to be lower than an absolute difference of ≥ 2 points for PID, but the expert was not aware of a minimally important difference specifically developed and validated in the population of interest. A working group of Outcome Measures in Rheumatology (OMERACT) suggested that pain trialists should report the percentage of patients achieving one or more thresholds of improvement from baseline pain —

specifically ≥ 20%, ≥ 30%, and ≥ 50% — to help contextualize the results;[26] although it is unclear whether these guidelines apply to the acute pain setting, as is the case with breakthrough pain. Nevertheless, the manufacturer conducted responder episode analyses that indicated that, as early as 10 minutes after treatment, a statistically greater proportion of breakthrough pain episodes treated with Fentora were characterized by ≥ 33% or ≥ 50% improvements in pain intensity versus placebo. The FDA also noted that the results from Study 14 met five of the six criteria developed by Farrar et al.[24] for determining clinical significance in an analgesic trial, concluding that Fentora provides a "statistically significant, clinically relevant" amount of analgesia for the proposed indication.[19] Still, it is important to highlight that none of the analyses were adjusted for multiplicity, which warrants caution in interpreting the results. The manufacturer also found, across both studies, that patients were over three times more likely to use rescue medication for a breakthrough pain episode for which placebo was used versus Fentora.

In the absence of direct data about the efficacy of Fentora versus other active treatments, the manufacturer submitted a network meta-analysis (NMA) to indirectly compare Fentora with morphine sulfate IR (MSIR), another fentanyl buccal tablet (FBT/2), FST, FBSF, fentanyl sublingual spray, fentanyl Ethypharm (FE), fentanyl pectin nasal spray, intranasal fentanyl spray (INFS), and OTFC. [redacted]. Of note, these effects might not be appreciable — the magnitude of the between-group difference in reduction in mean PID ranged from 0.60 to 1.05 on a 0 to 10 scale — and may occur too late in a breakthrough pain episode to be clinically significant. Other published NMAs generally indicate the same results as the one submitted by the manufacturer. In particular, one NMA found that INFS was associated with statistically significant reductions in PID versus Fentora at 15 and 30 minutes, but not at 45 and 60 minutes.[27] Two other NMAs found no statistically significant reductions in PID with Fentora versus MSIR at 15, 30, 45, and 60 minutes,[28,29] and one of them also demonstrated no statistically significant differences versus OTFC or MSIR at 15, 30, 45, and 60 minutes.[29]

4.2.2 Harms

At least 66% of the overall study population in each of the two trials experienced a 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% versus 47% in the titration period; 61% versus 55% in the treatment period — although the reason for these discrepancies was unclear. 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, per the manufacturer.

Notable harms that were commonly reported across Studies 14 and 3039 included dizziness, nausea, vomiting, and somnolence, all of which are AEs that are associated with all opioids, including fentanyl. Similarly, although the Health Canada product monograph for Fentora states that "fatal respiratory depression has occurred in patients treated with Fentora,"[14] there were no reported cases of respiratory depression in Studies 14 or 3039, and this potential harm is not unique to fentanyl. The manufacturer also conducted a long-term OL safety study of Fentora that found no new safety concerns relative to the Studies 14 or 3039, although several methodological limitations necessitate caution in interpreting the findings (0).

It should be noted that the manner in which Studies 14 and 3039 were designed precluded an assessment of the safety of Fentora versus placebo, because patients could have taken multiple tablets

in a single day, which would make it difficult, if not impossible, to attribute AEs observed over the entire duration of the study to a specific treatment. Furthermore, as noted by the FDA, there are several other challenges that limit the evaluation of the harms data from the two studies, including the fact that the trial patients were receiving opioids as ATC medication, they were allowed to use opioids for rescue medication, and that they comprised a relatively unhealthy population that was being treated with other highly toxic drugs.[18]

Over the course of Studies 14 and 3039, a total of 13 patients who took the study drug died, although, per the manufacturer, all deaths were considered not related or unlikely to be related to study drug treatment. There were 60 deaths after enrolment in the long-term safety study, all of which were attributable to disease progression. Overall, across the three studies — Studies 14, 3039, and the long-term safety study — a total of 73 (20%) patients died.

4.3 Other Considerations

Discussions with one of the consulting clinical experts highlighted several implementation issues with respect to Fentora. First, given that there is no method to directly convert the doses of Fentora to oral morphine equivalent, the expert raised concerns about the potential for errors in administering the appropriate strength of Fentora, which could lead to an increase in potential harm to patients. Second, Fentora contains fentanyl — a Schedule 1 controlled substance in Canada — which is susceptible to a similar level of abuse potential as other opioids, ultimately leading to fatal overdoses.[14] To this end, in April 2016, British Columbia declared a public health emergency after a "dramatic increase" in fatal overdoses from drugs such as fentanyl, with a similar declaration being called for in Alberta and Ontario.[30] Neither of the studies included in this review evaluated abuse, misuse, or diversion. Nevertheless, the spouse of a participant enrolled in a chronic non-cancer pain study of Fentora apparently pilfered and self-administered the participant's Fentora, and died due to respiratory depression. While there is no obvious reason to expect that fentanyl preparations such as Fentora would be subject to an increased risk of being abused or otherwise diverted compared with other IR opioid treatments, the manufacturer has developed a comprehensive Risk Minimization Action Plan (RiskMAP) that outlines plans for "appropriate intervention" should a concerning safety signal develop in the post-marketing period in the US.[18] Third, both experts consulted by the CDR team indicated that it would be extremely unusual for patients to have a contraindication to IR morphine, oxycodone, or hydromorphone but be able to tolerate Fentora, as the reimbursement request suggests.

4.4 Potential Place in Therapy

This information in this section is based on information provided in draft form by two clinical experts consulted by CDR reviewers for the purpose of this review.

Standard practice for managing patients with breakthrough cancer pain is to use the same opioid as that used to manage their baseline cancer pain, albeit in a different formulation. In Canada, commonly used opioids include morphine, oxycodone, and hydromorphone, each of which is available in short-acting formulations to be used to treat breakthrough pain; fentanyl is another available opioid analgesic. In general, opioids may be administered using a variety of routes, with the oral route being the most common and preferred route of administration. In cases where orally administering an opioid is inappropriate, as with patients who are unable to swallow, health care providers may use parenteral administrations, the most common of which is the subcutaneous route. Intravenous administrations may be used as well, although they are typically restricted to the intensive care unit setting. In Canada, at the present time, other than Fentora, only Abstral (a fentanyl product) is specifically indicated for the

management of breakthrough cancer pain, but it is not reimbursed by any public drug plans and is not used commonly in routine practice.

Given the Health Canada indication for Fentora, patients for whom Fentora is indicated would be those who have a diagnosis of active cancer and whose baseline cancer pain is responsive to continuous opioid therapy. However, the reimbursement request for Fentora suggests that the ideal patients may be those who are unable to swallow, or who have a contraindication to any of IR morphine, oxycodone, or hydromorphone, but who would otherwise be able to take Fentora. These patients would compose a very small proportion of the typical clinical population for which Fentora received regulatory approval. Given the numerous treatment options available, even if most are being used off label, there are no unfulfilled gaps to manage patients with breakthrough cancer pain. Indeed, from a clinical perspective, Fentora is unlikely to supersede all other oral and non-oral (subcutaneous, in particular) short-acting opioids that are currently used to manage patients with breakthrough cancer pain.

As with other opioids, any apparent benefits of Fentora must be weighed against its relative harms, particularly its abuse liability. Usually, opioids that cross the blood–brain barrier very fast, such as Fentora, are the ones that cause more euphoria, and consequently more physical dependence and addiction. Therefore, it would be important to assess, document, and treat opioid use disorder in the intended population. There might also be risks of misuse, overuse, overdose, and death if patients take Fentora in combination with other central nervous system–sedating substances, which is very common in these patients with cancer conditions.

5. CONCLUSIONS

Results from two RCTs — Study 14 (N = 77) and Study 3039 (N = 87) — suggest that, when compared with placebo, Fentora is associated with a statistically and clinically meaningful (as indicated by the responder episode analyses) improvement in PID as early as 10 minutes and lasting up to two hours after administration. Patients who were administered placebo were more likely to use rescue medication than Fentora-treated patients. Neither of the trials evaluated the effects of Fentora on the frequency of breakthrough pain episodes or HRQoL; nor did they assess its effects among patients with dysphagia or those who had lack of pain relief and/or intolerable opioid-related toxicities or AEs or contraindication to other IR opioids. The results of [redacted] published NMAs suggested that the analgesic effects of Fentora are similar to the effects of other opioids in managing breakthrough cancer pain. Data from Studies 14 and 3039 indicated that the safety profile of Fentora is consistent with that of other formulations of fentanyl and other opioids, and notable harms that were commonly reported among all patients in the two trials included dizziness, nausea, vomiting, and somnolence. There are no data to directly evaluate the relative safety of Fentora versus other active treatment options. Although fentanyl has a well-documented record of abuse, which is common to other IR opioids as well, neither of the included studies reported on abuse, misuse, or diversion with Fentora. A long-term OL safety study of Fentora did not reveal any new safety concerns relative to Studies 14 or 3039.

APPENDIX 1: PATIENT INPUT SUMMARY

No patient input was submitted for this review.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	August 9, 2016
Alerts:	Bi-weekly search updates until January 18, 2017
Study Types:	Randomized controlled trials, controlled clinical trials.
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
#	**Searches**	**Results**
1	exp fentanyl/	66172
2	exp fentanyl citrate/	16236
3	(fentanyl* or fentora* or abstral* or actiq* or breakyl* or duragesic* or durogesic* or durotep* or effentora* or fentaz* or ionsys* or lazanda* or leptanal* or matrifen* or onsolis* or oralet* or phentanyl* or fentanil* or fentanest* or rapinyl* or sentonil* or sublimaze* or subsys* or buquel*).ti,ab,kw.	49164
4	1 or 2 or 3	87790
5	buccal drug administration/ or exp sublingual drug administration/	8135
6	exp tongue/	46003
7	exp mouth mucosa/ or cheek mucosa/ or exp cheek/	79282
8	transmucosal drug administration/	87
9	(sublingual* or buccal* or transbuccal or trans mucosal or transmucosal or tongue* or mucous membrane* or cheek or cheeks).ti,ab,kw.	188091
10	((bioerodible or bio-erodible) adj2 mucoadhesive).ti,ab,kw.	19
11	5 or 6 or 7 or 8 or 9 or 10	260259
12	4 and 11	1676
13	conference abstract.pt.	2314907
14	12 not 13	1464
15	14 use oemezd	962
16	exp fentanyl/	66172
17	(fentanyl* or fentora* or abstral* or actiq* or breakyl* or duragesic* or durogesic* or durotep* or effentora* or fentaz* or ionsys* or lazanda* or leptanal* or matrifen* or onsolis* or oralet* or phentanyl* or fentanil* or fentanest* or rapinyl* or sentonil* or sublimaze* or subsys* or buquel*).ti,ab,ot,hw,kf,rn,nm.	86240
18	(437-38-7 or UF599785JZ or 80832-90-2 or 990-73-8 or MUN5LYG46H or (R adj "5240") or R5240 or R-5240 or R-4263 or R4263 or (R adj "4263")).rn,nm.	61217
19	16 or 17 or 18	88191
20	exp Administration, Sublingual/ or exp mouth mucosa/ or exp Administration, Buccal/	73669
21	cheek/	15235
22	(sublingual* or buccal* or transbuccal or trans mucosal or transmucosal or tongue* or mucous membrane* or cheek or cheeks).ti,ab,ot,sh,hw,rn,nm.	240464
23	((bioerodible or bio-erodible) adj2 mucoadhesive).ti,ab,ot,sh,hw,rn,nm.	20
24	20 or 21 or 22 or 23	285506
25	19 and 24	1701
26	25 use ppez	503
27	15 or 26	1465
28	exp animals/	42531038
29	exp animal experimentation/ or exp animal experiment/	1961411
30	exp models animal/	1399508
31	nonhuman/	4806228
32	exp vertebrate/ or exp vertebrates/	41324940
33	or/28-32	43997065
34	exp humans/	33724963
35	exp human experimentation/ or exp human experiment/	368589
36	or/34-35	33727066
37	33 not 36	10271603
38	27 not 37	1408
39	remove duplicates from 38	982

MULTI-DATABASE STRATEGY		
#	**Searches**	**Results**
40	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.	514850
41	Randomized Controlled Trial/	843296
42	exp Randomized Controlled Trials as Topic/	215779
43	"Randomized Controlled Trial (topic)"/	104987
44	Controlled Clinical Trial/	486514
45	exp Controlled Clinical Trials as Topic/	224896
46	"Controlled Clinical Trial (topic)"/	6846
47	Randomization/	159743
48	Random Allocation/	151786
49	Double-Blind Method/	237596
50	Double Blind Procedure/	133039
51	Double-Blind Studies/	232806
52	Single-Blind Method/	42960
53	Single Blind Procedure/	22659
54	Single-Blind Studies/	45263
55	Placebos/	269625
56	Placebo/	291871
57	Control Groups/	94014
58	Control Group/	94014
59	(random* or sham or placebo*).ti,ab,hw,kf,kw.	2732644
60	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	444555
61	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	1283
62	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.	907601
63	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	75301
64	allocated.ti,ab,hw.	108456
65	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	66371
66	or/40-65	3428644
67	39 and 66	291

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	5 August, 2016
Keywords:	Fentora (fentanyl buccal/sublingual tables), breakthrough cancer pain
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey Matters: A Practical Tool for Searching Health-Related Grey Literature" (https://www.cadth.ca/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Weinstein et al., 2009[31]	Study design — not RCT
Mercadante et al., 2011[32]	Study design — not RCT
Mercadante et al., 2012[33]	Comparator — study tested FBT using a titrated dosing strategy vs. FBT using a proportional dosing strategy, the latter of which is inconsistent with the approved indication
Kosugi et al., 2014[34]	Intervention —not Fentora
Zeppetella et al., 2010[35]	Study design — not RCT
Passik et al., 2014[36]	Population — mixed population; results of patient(s) with cancer pain not reported separately
Kleeberg et al., 2015[37]	Comparator — study tested FBT using a titrated dosing strategy vs. FBT using a proportional dosing strategy, the latter of which is inconsistent with the approved indication
Davies et al., 2015[38]	Study design — not RCT
Mercadante et al., 2015[39]	Intervention — study tested FBT using a proportional dosing strategy, which is inconsistent with the approved indication
Takigawa et al., 2015[40]	Study design — not RCT
Weinstein et al., 2009[41]	Study design — not RCT
Zhou et al., 2015[42]	Study design — not RCT
Zeppetella et al., 2015[43]	Study design — not RCT
Coluzzi et al., 2002[44]	Intervention — not Fentora (it was Actiq)
Coluzzi et al., 2002[45]	Intervention — not Fentora (it was Actiq)
Payne et al., 2001[46]	Intervention — not Fentora (it was OTFC)
Greenberg et al., 1996[47]	Study design — not RCT
Chidambaram et al., 1995[48]	Study design — not RCT
Mucke et al., 2016[49]	Intervention — study tested FBT using a titration dosing strategy that began with 200 mcg, which is inconsistent with the approved indication
Minkowitz et al., 2016[50]	Intervention — not Fentora (it was a fentanyl spray)
Corli et al., 2014[51]	Study design — not RCT
Bhatnagar et al., 2014[52]	Intervention — not Fentora (it was OTFC)
Rauck et al., 2015[53]	Intervention — not Fentora (it was a fentanyl spray)
Shimoyama et al., 2015[54]	Intervention — not Fentora (it was Abstral)
Shimoyama et al., 2015[55]	Intervention — not Fentora (it was Abstral)
Zeppetella et al., 2014[27]	Study design — not RCT
Velazquez Rivera et al., 2014[56]	Intervention — not Fentora (it was Abstral)
Zeppetella et al., 2013[57]	Study design — not RCT
Jandhyala et al., 2013[28]	Study design — not RCT
Webster et al., 2013[58]	Population — mixed population; results of patient(s) with cancer pain not reported separately
Guitart et al., 2013[59]	Study design — not RCT
Bornemann-Cimenti et al., 2013[60]	Study design — not RCT
Jandhyala et al., 2012[29]	Study design — not RCT
Nalamachu et al., 2012[61]	Study design — not RCT

Reference	Reason for Exclusion
Webster et al., 2011[62]	Study design — not RCT
Zeppetella et al., 2011[63]	Study design — not RCT
Nalamachu et al., 2011[64]	Study design — not RCT
Ashburn et al., 2011[65]	Population — mixed population; results of patient(s) with cancer pain not reported separately
Fine et al., 2010[66]	Population — patients had chronic non-cancer pain
Vissers et al., 2010[67]	Study design — not RCT
Rauck et al., 2009[68]	Intervention — not Fentora (it was Actiq)
Mercadante et al., 2009[69]	Intervention — not Fentora (it was Actiq)
Mercadante et al., 2007[70]	Intervention — not Fentora (it was Actiq)
Coluzzi et al., 2001[71]	Intervention — not Fentora (it was Actiq)
Portenoy et al., 1999[72]	Intervention — not Fentora (it was OTFC)
Farrar et al., 1998[23]	Intervention — not Fentora (it was Actiq)
Payne et al., 2001[73]	Intervention — not Fentora (it was Actiq)
Nabal et al., 2012[74]	Study design — not RCT
Wiffen et al., 2007[75]	Study design — not RCT
Schmidt-Hansen et al., 2015[76]	Study design — not RCT
Rodriguez et al., 2015[77]	Study design — not RCT
Guitart et al., 2015[78]	Study design — not RCT
Schmidt-Hansen et al., 2015[79]	Study design — not RCT
Wiffen et al., 2016[80]	Study design — not RCT

FBT = fentanyl buccal tablet; OTFC = oral transmucosal fentanyl citrate; RCT = randomized controlled trial.

APPENDIX 4: SUMMARY OF LONG-TERM SAFETY STUDY

1. Objective

To summarize a long-term open-label (OL) safety study that evaluated the tolerability and safety of Fentora in opioid-tolerant cancer patientspatients with cancer-related breakthrough pain.[31]

2. Findings

Study design

The long-term OL safety study was conducted in 47 centres in the US between April 2004 and November 2006 and involved three phases: screening (up to 14 days), titration (up to 21 days), and maintenance. The maintenance phase was originally designed for 12 months; however, an extension was added to continue the study through November 30, 2006, at which point Fentora became commercially available. Both Fentora-naive and Fentora-experienced individuals (rollover patients from Studies 14 and 3039, which are summarized in the main report)[15,16] were eligible for enrolment in the study. All patients continued to take their around-the-clock (ATC) opioid regimens for pain throughout the titration and maintenance phases. Of note, however, adjustments to the ATC dosing regimens were allowed.

Fentora-naive patients participated in the titration phase to identify a successful dose of Fentora (between 100 mcg and 800 mcg) to be used during the maintenance phase. A successful dose was defined as a dose that provided sufficient pain relief within 30 minutes for two consecutive episodes of breakthrough pain occurring at least four hours apart without unacceptable adverse events (AEs). During the titration phase, patients were required to wait four hours between Fentora doses; however, patients were allowed to take their standard supplemental medication if pain relief was not adequate within 30 minutes of taking Fentora. Prior to the titration phase, a 100 mcg test dose of Fentora was administered to patients not previously taking oral transmucosal fentanyl citrate (OTFC), as well as those taking ≤ 600 mcg of OTFC to assess tolerance, whereas patients taking 800 mcg, 1200 mcg, or 1600 mcg of OTFC were given test doses of 200 mcg, 400 mcg, or 600 mcg, respectively. Patients who did not achieve adequate relief of breakthrough pain at the highest successful dose of Fentora (800 mcg) discontinued the study. Rollover patients used the successful dose identified from previous randomized controlled trials (RCTs) and did not participate in the titration phase.

Patients who identified a successful Fentora dose were eligible to enter the maintenance phase during which they were able to take a second tablet of Fentora if pain relief was not adequate within 30 minutes of taking Fentora. If a participant required more than one tablet of Fentora for more than two breakthrough pain episodes per day, the investigator was able to increase the successful dose; however, if the participant was receiving the highest dose (i.e., 800 mcg), this participant was withdrawn from the study. During the maintenance phase, a maximum of eight tablets per day could be used to treat a maximum of six breakthrough pain episodes per day.

Patients were eligible to participate in the OL safety study if they met the following criteria:

- Were adults with pain associated with a histologically documented malignant solid tumour or a hematological malignancy and had a life expectancy ≥ 2 months
- Used a fixed-dose ATC opioid regimen; i.e., oral morphine at a dose of 60 mg to 1,000 mg/day or transdermal fentanyl at a dose of 25 mcg to 300 mcg/hour, or the morphine equivalent, for persistent cancer-related pain for ≥ 1 week

- Experienced an average of one to four episodes of breakthrough pain per day that were treated with a previously identified dose of Fentora (rollover patients) or other supplemental opioids (Fentora-naive patients)

Assessment

Safety was assessed by monitoring AEs, serious adverse events (SAEs), and withdrawals due to adverse events (WDAEs) at the end of the titration phase and monthly during the maintenance phase.

Patients recorded in a diary the number of breakthrough pain episodes and number of Fentora tablets taken per day. Patients also rated the efficacy of Fentora at improving breakthrough on a daily basis by using a global medication performance (GMP) assessment and completed the Patient Assessment of Medication questionnaire comparing Fentora to previous supplemental medications used to treat breakthrough pain before and one month after the maintenance phase. The GMP assessment and Patient Assessment of Medication questionnaire are not discussed in this report as they were not identified as relevant outcomes in the protocol. To assess the need for dose adjustments for either Fentora or ATC opioid regimens, the investigators reviewed participant diaries at each study visit focusing on the number of breakthrough pain episodes and tablets taken each day, as well as the use of any other supplemental medication for breakthrough pain management. Investigators also considered AEs when considering Fentora or ATC dose adjustments. Missing data were not imputed.

Results

A total of 232 patients were enrolled in the long-term OL safety study and were included in the overall safety population; i.e., received ≥ 1 dose of Fentora, of whom 110 (47%) were Fentora-naive and 122 (53%) were Fentora-experienced. Of the 112 patients in the titration phase, 79 (71%) achieved a successful Fentora dose and 77 (69%) entered the maintenance phase. Thirty-five (31%) patients discontinued the titration phase. A total of 197 patients (77 from the titration phase and 120 rollover patients) entered the maintenance phase, of whom 42 (21%) individuals completed the study, while 155 individuals (79%) discontinued during the maintenance phase. Participant disposition is detailed in Table 14. Baseline characteristics are detailed in Table 15 and are similar between the long-term OL safety study and Studies 14 and 3039; a notable exception is the use of oxycodone as a rescue medication — 35% in the OL safety study compared with 13% in Study 14 and 18% in Study 3039.

TABLE 14: PARTICIPANT DISPOSITION IN LONG-TERM SAFETY STUDY

	N (%)
Enrolled	**232**
Fentora-naive	110 (47)
Fentora-experienced	122 (53)
Titration phase	**112**
Fentora-naive	110
Fentora-experienced	2[a]
Achieved successful dose during titration period	79 (71)
Entered maintenance phase	77 (69)
Withdrew during titration phase	35 (31)
AE	6 (5)
Lack of efficacy	10 (9)
Consent withdrawn	11 (10)
Lost to follow-up	2 (2)
Other	6 (5)
Maintenance phase	**197**
Fentora-naive	0
Fentora-experienced	120 (61)
Completed maintenance	42 (21)[b]
Withdrew during maintenance phase	155 (79)
AE	70 (36)
Lack of efficacy	3 (2)
Consent withdrawn	29 (20)
Protocol violation	1 (< 1)
Lost to follow-up	3 (2)
Other	49 (25)[c]
Maintenance phase extension	**24**
Completed maintenance phase extension	16 (67)
Withdrew during maintenance phase extension	8 (33)
AE	1 (4)
Consent withdrawn	1 (4)
Other	6 (3)

AE = adverse event.
Note: Deaths were reported as discontinuations due to AEs. A total of 60 deaths were recorded after enrolment and were associated with cancer progression.
[a] Two rollover patients were re-titrated due to ineffective dose.
[b] A total of 42 patients were considered to have completed this study; however, exposure for 8 of these patients was < 360 days.
[c] Reasons for discontinuation included the following: discretion of the investigator (17), termination of the study by the sponsor (10), non-compliance (6) and lack of need for breakthrough pain medication (5), study drug was stolen (1), entered hospice (1), did not have cancer pain (1), was using additional opioids (1), took study drug as primary pain medication (1), terminated care (1), was excessively prescribed rescue medication (1), required a morphine pump (1), study site closed by the investigator (1), pregnancy (1), was taking more study drug than permitted (1).
Source: Weinstein et al.[31]

TABLE 15: SUMMARY OF BASELINE CHARACTERISTICS OF PATIENTS IN LONG-TERM SAFETY STUDY

Characteristic	Safety Population (N = 232)[a]
Age, mean (SD) (years)	55.3 (12.7)
Females, n (%)	122 (53)
Weight, mean (SD) (kg)	76.8 (21.0)
Height, mean (SD) (cm)	169.4 (11.3)
Race, n (%)	
White	195 (84)
Black	16 (7)
Other	21 (9)
Opioid used as ATC medication — overall	
n (%)	230
Mean (SD) morphine equivalent (mg/day)	241.0 (384.4)
Median (min, max)	160 (5.0, 4800.0)[b]
Opioid used as ATC medication — specific drugs, n (%)	
Oxycodone	83 (36)
Fentanyl	77 (33)
Morphine	61 (27)
Methadone	21 (9)
Opioid used as rescue medication — overall	
n (%)	220
Mean (SD) morphine equivalent (mg/breakthrough pain episode)	20.2 (17.2)
Median (min, max)	15.0 (1.0, 160.0)
Opioid used as rescue medication — specific drugs, n (%)	
Oxycodone	78 (35)
Hydrocodone/acetaminophen	62 (28)
Morphine	29 (13)
Hydromorphone	28 (13)
Fentanyl citrate	15 (7)

ATC = around-the-clock; SD = standard deviation.
Note: Patients may have reported more than 1 drug for ATC and rescue medication. No ATC data and no supplemental medication data were available for 2 patients and 10 patients, respectively. Supplemental medication was not an opioid for 1 participant and the dose and frequency was not confirmed for 1 participant.
[a] Includes all patients who received ≥ 1 dose of Fentora after enrolment.
[b] Four patients were receiving < 60 mg/day of oral morphine equivalents and were considered protocol violations.
Source: Weinstein et al.[31]

Exposure

Similar to the previous RCTs, of the patients who entered the maintenance phase in the long-term OL safety study, the most commonly identified successful dose was the highest dose of Fentora (i.e., 800 mcg) — specifically, 31% and 35% of patients in Studies 14 and 3039, respectively, and 46% in the long-term OL safety study. The mean standard deviation (SD) duration of exposure to Fentora was 6.5 (6.5) days in the titration phase and 181.5 (168.3) days in the maintenance phase. A total of 61%, 38%, and 18% of patients were exposed to ≥ 3 months, ≥ 6 months, and ≥ 12 months of Fentora in the long-term OL safety study, respectively. Exposure and dosing are detailed in Table 16 and Table 17, respectively.

TABLE 16: EXPOSURE TO FENTORA IN LONG-TERM SAFETY STUDY

Parameter	Safety Population (N = 232)	
	Titration (N = 112)	Maintenance (N = 197)
Duration of exposure (days)		
Mean (SD)	6.5 (6.5)	181.5 (168.3)
Median (min, max)	5 (1, 46)	122 (1, 698)
Patients exposed to Fentora, n (%)[a]		
≥ 3 months	NA	121 (61)
≥ 6 months	NA	74 (38)
≥ 12 months[b]	NA	36 (18)

SD = standard deviation
[a] Months were determined based on exposure in days; ≥ 360 days were considered as ≥ 12 months.
[b] A total of 42 patients were considered to have completed this study; however, exposure for 8 of these patients was < 360 days, and they are not counted in this table. In addition, 2 patients who completed 12 months of treatment were not considered to have completed the maintenance phase (1 participant died and 1 participant discontinued treatment).
Source: Weinstein et al.[31]

TABLE 17: DOSE ADJUSTMENT FROM THE ORIGINAL SUCCESSFUL DOSE TO THE FINAL DOSE AT THE LAST STUDY VISIT IN LONG-TERM SAFETY STUDY (MAINTENANCE PHASE)

Final Dose	Successful Dose, n (%)[a]					
	100 mcg (n = 15)	200 mcg (n = 26)	400 mcg (n = 43)	600 mcg (n = 51)	800 mcg (n = 62)	Total (n = 197)
100 mcg (n = 11)	11 (73)	0	0	0	0	11 (6)
200 mcg (n = 20)	2 (13)	15 (58)	2 (5)	1 (2)	0	20 (10)
400 mcg (n = 35)	1 (7)	8 (31)	23 (53)	3 (6)	0	35 (18)
600 mcg (n = 39)	1 (7)	2 (8)	9 (21)	26 (51)	1 (2)	39 (20)
800 mcg (n = 92)	0	1 (4)	9 (21)	21 (41)	61 (98)	92 (46)

[a] Successful Fentora doses were identified during the titration phase (in treatment-naive patients) or during the previous studies (rollover patients).
Source: Weinstein et al.[31]

Safety

Generally, more patients experienced AEs in the maintenance phase than in the titration phase (93% versus 61%) (Table 18). In contrast, more patients experienced AEs related to Fentora in the titration phase than in the maintenance phase (46% versus 38%). The most common AEs related to Fentora (≥ 10%) according to the investigator during the maintenance phase were nausea (10%), constipation (8%), dizziness (6%), and somnolence (6%).

According to the investigator, all SAEs were considered to be related to the patients' underlying conditions and were considered not related or unlikely to be related to the study drug with the exception of one (drug withdrawal syndrome).

A total of 77 (33%) patients withdrew due to AEs, of whom six patients (5%) withdrew during the titration phase and 71 (36%) during the maintenance phase. Of the withdrawals during the maintenance phase, 53 (69%) were related to the patients' underlying conditions and considered not related or unlikely to be related to the study drug according to the investigator.

Overall, there were a total of 60 deaths in the long-term OL safety study, all of which were attributable to progression of cancer or pathology of the underlying conditions and considered not related or unlikely to be related to the study drug, according to the investigator.

Notable harms, such as nausea, vomiting, dizziness, fatigue, constipation, and somnolence, are among the most common AEs occurring in 37% of patients for nausea, 22% of patients for vomiting, 20% of patients for dizziness, 16% of patients for fatigue, 14% of patients for constipation, and 13% of patients for somnolence. There were no reported cases of respiratory depression and no reported incidences of overdose.

TABLE 18: SUMMARY OF ALL ADVERSE EVENTS

	Safety Population		
	Titration (N = 112)	**Maintenance (N = 197)**	**Overall (N = 232)**
Patients with > 0 AEs, n (%)	68 (61)	184 (93)	208 (90)
Withdrawals due to AEs, n (%)	6 (5)	71 (36)	77 (33)
Number of deaths, n (%)	2 (2)	58 (29)	60 (26)
AEs occurring in 5% of patients, n (%)			
Nausea	27 (24)	63 (32)	86 (37)
Vomiting	4 (4)	48 (24)	52 (22)
Dizziness	29 (26)	21 (11)	46 (20)
Fatigue	3 (3)	35 (18)	38 (16)
Constipation	3 (3)	30 (15)	33 (14)
Somnolence	14 (13)	18 (9)	30 (13)

AE = adverse event.
Note: This table is not limited to treatment-emergent adverse events. Patients may have indicated more than one AE.
Source: Weinstein et al.[31]

Limitations

There are several limitations to this long-term OL safety study. First, given that it was an uncontrolled study, it remains unclear whether the changes observed in the safety profile were due to a natural course of the disease or were attributed to long-term treatment with Fentora. OL trial designs in which both the investigators and the patients are unblinded to treatment allocation may have an impact on subjective outcomes, such as some participant-reported AEs. Additionally, dose adjustments for both ATC and Fentora regimens were permitted during the study; this makes it difficult to isolate the safety profile of Fentora. Finally, this study permitted patients to utilize doses that are not reflective of the dosage regimens recommended in the Health Canada product monograph; in particular, patients were permitted to take up to two Fentora tablets within 30 minutes of a breakthrough pain episode for a maximum of eight tablets per day, whereas Health Canada limits this to one Fentora per breakthrough pain episode, for a maximum of four tablets per day. Given that these doses are greater than those recommended in Canada, the true safety profile remains unclear, and the generalizability of the results to the Canadian population is in question.

3. Summary

In general, treatment with Fentora raised no new safety concerns relative to the previous RCTs. However, any inferences based on this long-term OL safety study should be made with caution given its limitations.

APPENDIX 5: SUMMARY OF INDIRECT COMPARISONS

Introduction

Background

There is no direct evidence on the efficacy of Fentora versus active therapies, as the manufacturer submitted two studies that evaluated Fentora versus placebo, and no additional studies were identified among the results of the literature search conducted by the CADTH Common Drug Review (CDR).

The aim of this section is to identify, summarize, and critically appraise indirect comparisons (IDCs) that provide evidence for the efficacy and harms of Fentora versus active therapies 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.

Methods

One IDC submitted by the manufacturer was reviewed.[81] Additional IDCs published in the literature were sought among the results of the literature search conducted by the CDR review team for the main clinical review report.

Description of Indirect Comparisons Identified

One IDC was submitted by the manufacturer and no published IDCs were identified in the literature search.

Review and Appraisal of Indirect Comparisons

Review of manufacturer's indirect comparison

Objectives and rationale for manufacturer's indirect comparison

The primary objective of the manufacturer's IDC was to establish the comparative efficacy and safety of fentanyl buccal tablet (FBT) versus [redacted].

Methods for manufacturer's indirect comparison

Study eligibility and selection process

Literature search

[redacted]

Eligibility criteria

[redacted]

Study selection

[redacted]

Data extraction

[redacted]

Comparators

[redacted]

Outcomes

[redacted]

(Section 2.2, Table 3).

[redacted]

Quality assessment of included studies

[redacted]

Indirect comparison methods

[redacted]

[redacted]

[redacted]

Results

Included studies

[redacted] (Figure 7).

FIGURE 7: EVIDENCE NETWORK FOR PRIMARY ANALYSIS

Source: Redwood Outcomes.[81]

[redacted]

[redacted]Figure 8.

FIGURE 8: BASELINE CHARACTERISTICS OF PATIENTS ENROLLED THE INCLUDED STUDIES INCLUDED IN THE PRIMARY ANALYSIS

Source: Redwood Outcomes.[81]

[redacted]Figure 9.

FIGURE 9: EVIDENCE NETWORK FOR SENSITIVITY ANALYSIS

Source: Redwood Outcomes.[81]

[redacted]

Efficacy

[redacted](Table 19).

TABLE 19: EFFECT OF FENTORA VERSUS OTHER TREATMENTS ON [redacted] AT [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]

[redacted]

Note: Statistically significant results are bolded.
Source: Redwood Outcomes.[81]

[redacted] (Table 20). [redacted]

TABLE 20: EFFECT OF FENTORA VERSUS OTHER TREATMENTS ON [redacted] AT [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]

[redacted].

Note: Statistically significant results are bolded.
Source: Redwood Outcomes.[81]

[redacted] (Table 21). [redacted]

TABLE 21: EFFECT OF FENTORA VERSUS OTHER TREATMENTS ON [redacted] AT [redacted]

[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]

[redacted]

Note: Statistically significant results are bolded.
Source: Redwood Outcomes.[81]

[redacted] (Table 22). [redacted]

TABLE 22: EFFECT OF FENTORA VERSUS OTHER TREATMENTS ON [redacted] AT [redacted]

[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]

[redacted]

Note: Statistically significant results are bolded.
Source: Redwood Outcomes.[81]

Harms

[redacted]

Table 23. [redacted]

TABLE 23: FREQUENCY OF [redacted]

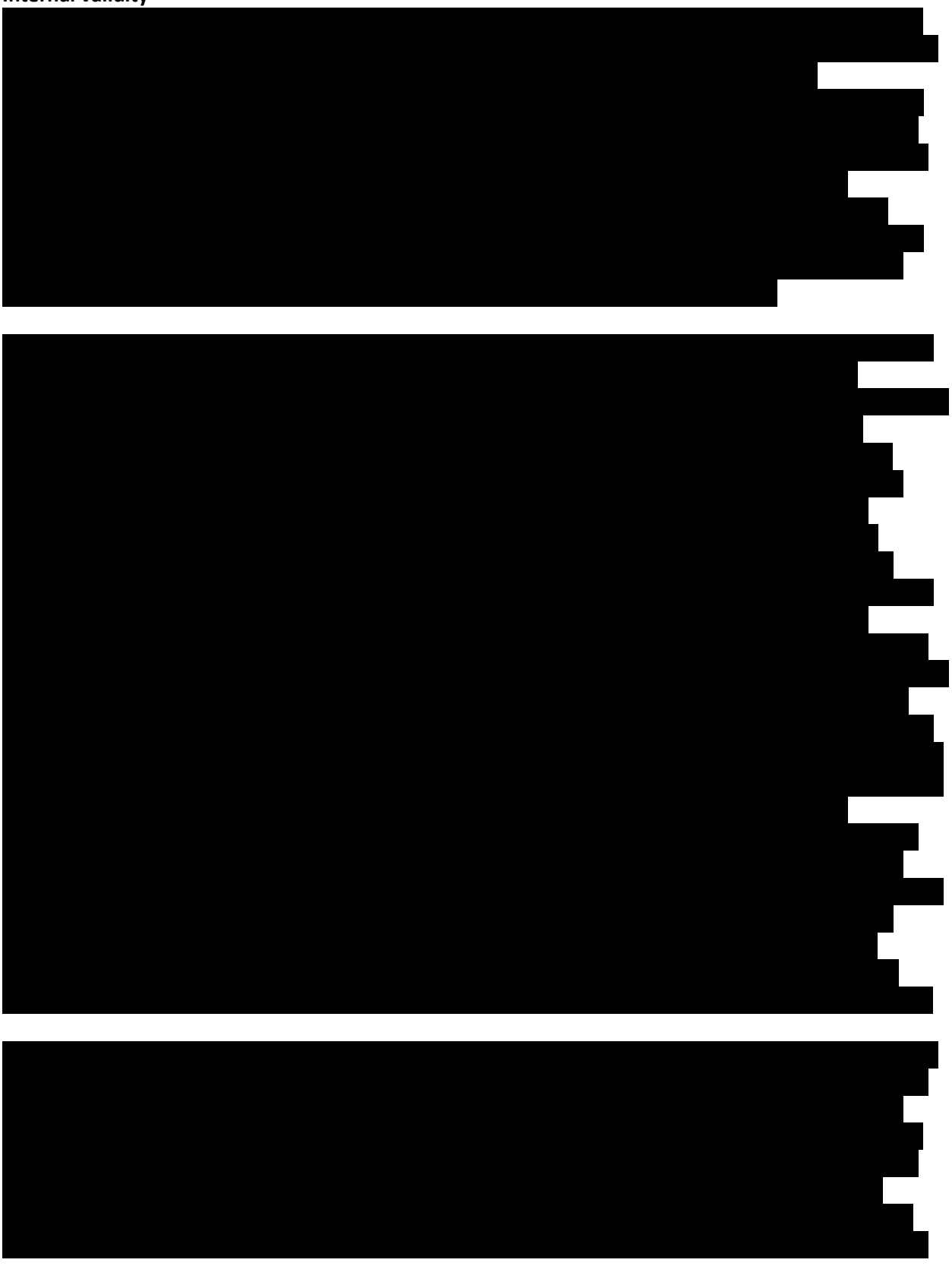
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Note: The numerical values in the table represent point estimates and 95% confidence intervals.
Source: Redwood Outcomes.[81]

Critical appraisal

Internal validity



[redacted]

[redacted]

External validity

[redacted]

Conclusion

The results of [redacted] published network meta-analyses suggested that the analgesic effects of Fentora are similar to the effects of other opioids in managing breakthrough cancer pain.

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