Common Drug Review
Pharmacoeconomic 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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ABBREVIATIONS

AUC	area under the (pain intensity) curve
BTCP	breakthrough cancer pain
CDR	CADTH Common Drug Review
CI	confidence interval
CUA	cost-utility analysis
FEBT	fentanyl effervescent buccal tablet
HAS	Haute Autorité de Santé
HTA	health technology assessment
ICUR	incremental cost-utility ratio
MSIR	morphine sulfate immediate-release
NMA	network meta-analysis
PBAC	Pharmaceutical Benefits Advisory Committee
PID	pain intensity difference
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SMC	Scottish Medicines Consortium

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	FEBTs (Fentora)
Study Question	"The objective of this study was to assess the cost-effectiveness of fentanyl buccal tablets (Fentora), as compared with usual care, in the treatment of breakthrough cancer pain. The analysis was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care."
Type of Economic Evaluation	Cost-utility analysis
Target Population	*Health Canada indication:* 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. *Reimbursement request:* Cancer patients aged 18 years or older, with underlying pain adequately managed with a continuous opioid (e.g., morphine or transdermal fentanyl), and who met one or more of the following criteria: • 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 swallowing. Of note, the effectiveness data used for the pharmacoeconomic analysis were aligned with the Health Canada indication and not the reimbursement request.
Treatment	FEBTs
Outcome	QALYs
Comparator	MSIR (20 mg oral tablet)
Perspective	Canadian publicly funded health care system
Time Horizon	181.5 days — based on mean duration of exposure to FEBT reported in an open-label extension of Study 14 and Study 3039
Results for Base Case	ICUR = $91,592 per QALY
Key Limitations	• Patients on MSIR were assumed to incur the costs of MSIR but only experienced the effectiveness of placebo (based on the pivotal phase III trial results from Study 14 and Study 3039). This serves to bias cost-effectiveness estimates in favour of FEBT. • Uncertainty regarding the duration of treatment benefit with FEBT. The manufacturer's base-case assumptions were unsupported and served to bias cost-effectiveness results in favour of FEBT. • Concerns relating to the clinical evidence, including low external validity of the results from the pivotal trials, which may bias the cost-effectiveness estimates, and uncertainty in the results of the manufacturer's network meta-analysis. • Uncertainty in daily frequency of BTCP episodes. • Uncertainty in calculated QALYs, including use of mapped utility values from non-Canadian sources and unclear clinical meaningfulness of differences between FEBT and MSIR. • Drug costs for FEBT do not include costs of initial or further titration. Given the flat pricing across dosage forms, this may result in higher daily costs than currently modelled.

CDR Estimate(s)	• To account for some of the above limitations (use of MSIR efficacy values for MSIR, assuming that patients experienced 4 BTCP episodes per day, and that the benefits of FEBT lasted for the duration of the BTCP episode [1 hour] and 1 additional hour beyond that [duration of treatment effect was assumed to be 2 hours]), CDR estimated the ICUR of FEBT vs. MSIR is $617,293 per QALY. At the submitted price, there is a 0% probability of FEBT being cost-effective at both willingness-to-pay thresholds of $50,000 and $100,000 per QALY. This ICUR is likely an underestimation, as it does not take into account the potential higher drug cost from titration. • A price reduction of 85% is necessary for FEBT to achieve an ICUR of $50,000 per QALY vs. MSIR in CDR's base case. • Of note, there were concerns regarding the external validity of the results from the pivotal trials, which may bias cost-effectiveness estimates. In particular, the trial population likely represented a less severe population with more easily managed pain than would be seen in clinical practice. As such, the ICURs for both the manufacturer and CDR base cases are likely underestimated.

BTCP = breakthrough cancer pain; CDR = CADTH Common Drug Review; FEBT = fentanyl effervescent buccal tablet; ICUR = incremental cost-utility ratio; MSIR = morphine sulfate immediate-release; QALY = quality-adjusted life-year.

EXECUTIVE SUMMARY

Background

Fentanyl effervescent buccal tablets (FEBTs; brand name Fentora) are an oral formulation of the opioid analgesic fentanyl. FEBT is indicated for the management of breakthrough cancer pain (BTCP) 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.[1] The manufacturer is requesting that FEBT be reimbursed for the management of breakthrough pain in advanced cancer patients aged 18 years or older with the underlying pain adequately managed using a continuous opioid therapy (for persistent baseline cancer pain) and one or more of:

- Lack of adequate pain relief and/or intolerable opioid-related toxicities, adverse events, or contraindication to other short-acting/immediate-release opioids (i.e., morphine, oxycodone, or hydromorphone) and/or
- Difficulty swallowing (dysphagia).

FEBT is available in 100, 200, 400, 600, and 800 mcg tablets at a price of $10.89 per tablet for all strengths. At a recommended dose of up to 800 mcg per episode of breakthrough pain and assuming up to four episodes per day, FEBT costs $10.89 to $43.56 per day. Of note, this assumes that patients' doses are optimized to the correct dose required per episode and does not account for the possible use of multiple tablets during the titration phase, as suggested by the product monograph.[1]

The manufacturer submitted a cost-utility analysis comparing FEBT to usual care (defined as morphine sulfate immediate-release [MSIR] 20 mg oral tablet) for the management of BTCP among cancer patients who met the reimbursement request criteria: lack of adequate relief or intolerable toxicity, adverse events or contraindication to short-acting/immediate-release opioids (morphine, oxycodone, hydromorphone), and/or dysphagia.[2] The analysis was based on a decision tree applying a time horizon of 181.5 days and was undertaken from the perspective of the Canadian publicly funded health care system. Treatment effectiveness data (defined by pain intensity reduction from baseline) were derived from a manufacturer-commissioned network meta-analysis (NMA).[3] Costs considered were drug acquisition costs and costs of emergency department visits. Treatment-specific utility scores were based on mapping pain intensity to utilities using a linear regression model informed by UK data. The manufacturer reported that, compared with usual care, use of FEBT was associated with an incremental cost-utility ratio (ICUR) of $91,592 per quality-adjusted life-year (QALY).

Summary of Identified Limitations

The CADTH Common Drug Review (CDR) identified several key limitations in the manufacturer's economic submission. Firstly, patients on MSIR were assumed to incur the costs of MSIR but only experienced the effectiveness of placebo — this approach is inappropriate and biases the results in favour of FEBT. Secondly, there was uncertainty regarding the duration of treatment benefit with FEBT relative to the length of a BTCP episode. The manufacturer assumed that patients experienced the benefits of FEBT over the course of 24 hours and this was modelled as patients experiencing treatment-specific BTCP utilities continuously without ever returning to baseline background pain. This contradicts the clinical definition of BTCP (i.e., transitory exacerbations of pain occurring despite a background of adequately controlled pain)[4] and is unsupported by data. Such an approach further serves to bias the cost-effectiveness results. Thirdly, there were concerns regarding the generalizability of the results from the phase III pivotal trials, because of high dropout rates and stringent inclusion and exclusion criteria that likely resulted in the assessment of FEBT in a less severe population than would be seen in clinical

practice. [redacted]. Given these limitations, ICURs (both the manufacturer's and CDR's) are likely underestimated relative to what would be seen in clinical practice. Further limitations include uncertainty regarding the daily frequency of BTCP episodes, and uncertainty with respect to computed QALYs.

Key Results and Conclusions

Based on reanalyses to account for some of the above limitations (replacement of placebo efficacy values with MSIR efficacy values for MSIR, assuming that patients experienced four BTCP episodes per day and that the benefits of FEBT lasted for the duration of the BTCP episode [one hour] and one additional hour beyond that [duration of treatment effect was assumed to be two hours]), CDR estimated that the ICUR of FEBT versus MSIR is likely greater than $617,293 per QALY. At the submitted price, there is a 0% probability of FEBT being cost-effective at both willingness-to-pay thresholds of $50,000 and $100,000 per QALY. However, CDR's ICUR is likely an underestimation as it does not take into account the potential higher drug cost from titration.

Of note, there were concerns regarding the external validity of the results from the pivotal trials, which may bias cost-effectiveness estimates. In particular, the trial population likely represented a less severe population with more easily managed pain than would be seen in practice. Given that these patients likely demonstrate more favourable clinical response to FEBT than would be seen in practice, the ICURs produced in both the manufacturer and CDR base cases are possibly underestimates of the true cost-effectiveness of FEBT.

At the submitted price of $10.89 per tablet, a price reduction of at least 85% would be necessary in CDR's base case to achieve the same ICUR.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis (CUA) based on a decision-tree model comparing fentanyl effervescent buccal tablets (FEBTs) to usual care (which consisted of the placebo response from the manufacturer's network meta-analysis [NMA] and the costs of a 20 mg oral tablet of morphine sulfate immediate-release [MSIR]) for the treatment of breakthrough cancer pain (BTCP) among cancer patients with adequately managed background pain who fulfill one or more of the reimbursement request criteria:

- Inadequate relief or intolerable toxicity, adverse events, or contraindication to short-acting/immediate-release (IR) opioids (morphine, oxycodone, or hydromorphone), and/or
- Dysphagia.

The base case assumed that patients experienced three episodes of BTCP per day (each lasting one hour) over a time horizon of 181.5 days (based on mean duration of exposure to FEBT reported in a long-term open-label study assessing safety of FEBT).[5] The analysis was undertaken from the perspective of the Canadian publicly funded health care system.

Patients received either one tablet of FEBT (dosage not specified) or usual care at the onset of a BTCP episode. Analgesic efficacy of FEBT and usual care were expressed as expected reductions in pain intensity from baseline at 15, 30, 45, and 60 minutes after onset of a BTCP episode. When plotted as pain intensity curves (Figure 1), these represent the course of pain intensity over a BTCP episode for each treatment. More effective treatments result in lower pain intensities over the course of the episode, and as a result the total area under the curve (AUC) per BTCP episode is lower than that of a less effective treatment. Conceptually, the difference between AUCs reflects the amount of BTCP avoided by the intervention. Efficacy data for each time point were derived from a manufacturer-sponsored NMA that included four studies comparing FEBT and MSIR in controlling BTCP,[3] while values for placebo were plotted using values from the two pivotal phase III trials.[6,7] Reductions in pain intensity were used to estimate quality-adjusted life-years (QALYs) and inform estimates of resource use for each treatment. While the manufacturer provided efficacy data for MSIR, it opted to use placebo values for the efficacy of usual care (which was costed as MSIR). This was justified by appealing to the manufacturer's reimbursement request (patients with inadequate relief, toxicity, adverse events, or contraindication to short-acting/IR opioids). It was assumed that in this population, MSIR would be ineffective and thus have equivalent efficacy to placebo.

Treatment-specific utility values were based on pain intensity curves and their AUCs. The function linking pain intensity and utility was based on a linear regression model derived from a UK study that directly elicited utility values from the general population using the time-trade-off method. Adverse events were not considered, as they were assumed to be similar between FEBT and MSIR. The manufacturer assumed that the treatment-specific utility value applied 24 hours a day (i.e., that treatment benefits extend beyond episodes themselves to the time between episodes).

Costs considered in the base case were drug acquisition costs and the costs of emergency department visits. Drug costs were based on the manufacturer-submitted price for FEBT, while costs of MSIR came from the Ontario Drug Benefit Formulary.[8] The manufacturer assumed that use of FEBT would avert one

pain-related emergency department visit over the course of the model, based on expert opinion. The costs of emergency department visits were based on Hospital Data Blitz sources cited by the manufacturer. In a scenario analysis, the manufacturer considered possible effects on other types of health care resources (emergency department visits, hospitalizations, and palliative care physician visits). Adverse events were not considered, as it was assumed that they were similar between treatments. Because of the short time horizon, neither costs nor outcomes were discounted.

2. MANUFACTURER'S BASE CASE

From the public payer perspective, the manufacturer reported in its base-case analysis that FEBT is associated with a cost of $5,930 and 0.22 QALYs. When compared with usual care, FEBT was $5,394 more costly and associated with 0.06 additional QALYs for an incremental cost-utility ratio (ICUR) of $91,592 per QALY (details available in Table 11 in Appendix 5).

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Among the manufacturer's reported sensitivity analyses, results were most sensitive to duration of treatment benefit. If treatment-specific utility values were applied only for the duration of the BTCP episode (i.e., one hour) rather than 24 hours, then the ICUR would increase to $732,735 per QALY. When assuming that usual care had the cost and effectiveness of MSIR, the manufacturer's base-case ICUR increased to $151,860 per QALY. This increased to $1,214,881 per QALY when assuming that treatment benefit duration was limited to the BTCP episode (one hour). Further sensitivity analyses of interest were assumptions regarding effectiveness of FEBT (range: $45,192 to $130,846 per QALY when using data from a recent randomized controlled trial [RCT] from Mercadante et al.[9] and assuming 30% lower efficacy of FEBT, respectively) and impact of pain on utility (range: $80,928 to $113,299 per QALY for higher and lower impacts of pain on utility, respectively, although the manufacturer did not specify how these analyses on utilities were undertaken).

The manufacturer also reported the results of a probabilistic sensitivity analysis (PSA) that reported a higher ICUR than the base case ($250,000 per QALY). At a willingness-to-pay threshold of $100,000 per QALY, FEBT had a 4% probability of being cost-effective. At a reduced price ($4 per episode), FEBT became cost-effective 61% of the time at a willingness-to-pay threshold of $100,000 per QALY. The PSA was based on 1,000 iterations. This was found to be a sufficient number of simulations to ensure stability of results.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Assumption that morphine sulfate immediate-release has the same efficacy as placebo is not warranted and serves to bias cost-effectiveness results in favour of fentanyl effervescent buccal tablet**

  In its base case, the manufacturer assumed that patients incurred the costs of MSIR but only the efficacy of placebo; this was justified by appealing to the reimbursement request (i.e., patients did not get adequate pain relief from short-acting opioids and thus would have similar effectiveness to placebo). However, such an approach is unwarranted for a number of reasons:
  - As per the CADTH Common Drug Review (CDR) submission guidelines, the manufacturer should include as part of its submission a "pharmacoeconomic evaluation for the full population identified in the approved Health Canada indication(s) to be reviewed by CDR."[10] The full Health Canada indication for FEBT does not include any reference to patients who have intolerance, lack of efficacy, or contraindication to short-acting/IR opioids.

- The manufacturer's reimbursement request notes that patients should experience a lack of adequate pain relief, intolerable toxicity, adverse events, or contraindication to any of the following opioids: morphine, oxycodone, and hydromorphone. Thus, for patients who have failed on hydromorphone or oxycodone, MSIR remains an option.
- Finally, the clinical trial populations in the two pivotal trials [6,7] did not assess patients who were intolerant of, contraindicated to, or uncontrolled on a short-acting/IR opioid.

Given the above considerations, use of MSIR efficacy values are considered the preferred base-case assumption in CDR's reanalyses. CDR acknowledges that there is heterogeneity in practice within this clinical area as specified by CDR clinical experts. CDR concluded that short-acting/IR oral opioids are the most relevant comparator, based on the Health Canada indication, and on the population assessed by the model. Nevertheless, subcutaneous preparations of fentanyl and intravenous morphine may also be appropriate comparators, especially considering that the reimbursement request criteria specify patients with dysphagia. However, these are most generally used in a hospital setting and are limitedly used in the community, as explained by CDR clinical experts.

- **Assumptions regarding length of treatment effect are uncertain**
  The manufacturer assumed that the treatment benefits of FEBT would extend beyond the duration of three one-hour episodes of BTCP, resulting in an improvement to patients' quality of life 24 hours a day. This was modelled as patients continuously experiencing treatment-specific BTCP utilities (utility of a BTCP episode on FEBT and MSIR being 0.37 and 0.29, respectively) without experiencing any period of time with the utility score associated with baseline pain (0.67). This approach was justified by reference to a previous economic evaluation[11] that implicitly made use of the same approach without justification. There are numerous problems with this approach:
  - The only evidence for a beneficial effect of FEBT beyond the duration of a BTCP episode was from Study 3039,[7] in which analgesic efficacy relative to placebo was observed at two hours after onset of an episode. Quality-of-life data were not collected during the course of the clinical trials.
  - The assumption that patients continuously experience treatment-specific BTCP utility and no period of time with the utility score of background pain produces the counterintuitive result that more long-lasting positive effects on quality of life produce lower QALYs — this lacks face validity. Further, the definition of BTCP includes reference to its transitory nature against a constant background of baseline pain[4] — experiencing constant BTCP-related utility does not reflect the clinical nature of BTCP.

  While CDR acknowledges a paucity of data and high levels of uncertainty relating to the effects of BTCP control on broader quality of life, the assumption of 24-hour benefit is unsupported by any evidence and is lacking in face validity. CDR's preferred assumption, based on the results of Study 3039,[7] is that the duration of treatment benefit spans the length of a BTCP episode (one hour) plus an additional hour afterward, for a total of two hours, prior to returning to baseline pain and quality of life. A range of different assumptions relating to duration of treatment benefit were further explored (Table 14, Table 15).

- **Concerns regarding generalizability of results from pivotal trials as a result of low external validity and consequently biased cost-effectiveness estimates**
  As noted in CDR's Clinical Review Report, there are numerous concerns relating to the questionable external validity of the study populations in Studies 14 and 3039:[6,7]

- A substantial percentage of participants (37.4% in Study 14; 29.5% in Study 3039)[6,7] withdrew from the studies during the titration period, which limits the clinical population to which the results of the studies may be directly applied. Further, given that 16.3% of patients in Study 14[6] withdrew due to inability to achieve analgesia even at 800 mcg FEBT, the population included in the double-blind phase may be less severe than the population that would be seen in practice.
- Exclusion criteria were restrictive enough to be of concern. The clinical expert emphasized that it would be unlikely to find a patient in a typical pain management practice in Canada who would not be experiencing neurological or psychiatric impairment. It would also be unlikely that patients would be screened for sleep apnea or a history of substance abuse. All of these were used as exclusion criteria.
- The study populations do not reflect the manufacturer's reimbursement request criteria — for instance, there was no requirement for trial participants to have dysphagia or intolerance or contraindication to other short-acting/IR opioids.
- Enrolment was limited to patients who experienced one to four episodes of BTCP daily, although both of CDR's consulting clinical experts and literature sources[12] state that this is likely lower than the daily frequency that would be seen in practice.

The above considerations point to a less severe population with more easily managed pain than would be seen in clinical practice — a point confirmed by CDR's clinical experts. Given that these patients likely demonstrate more favourable clinical response to FEBT than would be seen in the clinical population, ICURs produced in both the manufacturer and CDR base cases are possibly underestimates of the true cost-effectiveness of FEBT.

[redacted] Further, there was no subgroup analysis reflecting the requested reimbursement population.

- **Assumptions regarding number of breakthrough cancer pain episodes a day are uncertain**
  In the manufacturer's base case, it was assumed that patients experienced three episodes of BTCP per day, and in the pivotal trials, enrolment was restricted to patients experiencing one to four episodes per day.[6,7] However, literature sources[12] and CDR's consulting clinical experts noted that this is possibly an underestimate and that patients are more likely to experience four to six episodes per day. CDR's preferred base-case assumption is that patients experience four episodes per day, but a range of episode frequencies was assessed in sensitivity analyses (Table 13, Table 15).

- **Uncertainty with respect to calculated quality-adjusted life-years**
  Treatment-specific utility values were based on a linear regression-based mapping based on a British study, linking areas under the pain intensity curve to utilities. However, the use of a mapping based on responses from a British population introduces uncertainty into calculated QALYs. Further, quality-of-life data were not collected in the phase III studies.[6,7] The manufacturer conducted sensitivity analyses on the impact of BTCP on utilities and found that this was not a key driver of results; however, it is unclear how these analyses were carried out. A further concern is the questionable clinical meaningfulness of pain intensity reduction versus MSIR, as observed in the NMA. The magnitude of between-group difference in reduction in mean pain intensity ranged from 0.22 to 1.05 on a 0 to 10 scale. Further, these results became statistically significant only at 45 and 60 minutes after onset of an episode, which may be too late into an episode to be clinically

meaningful. These results cease to be statistically significant when considering a random-effects model. As such, calculated quality-of-life differences between FEBT and MSIR should be considered with some skepticism.

- **Drug costs of FEBT do not include costs of initial or further titration, leading to possible underestimates of daily costs of FEBT**
  As per the product monograph,[1] patients are to begin titration at a dose of 100 mcg per episode and are to titrate upward to an effective dose using multiple 100 mcg tablets (up to a dose of 400 mcg). Beyond 400 mcg, patients are instructed to use multiple 200 mcg tablets (for 600 mcg and 800 mcg doses). Given the flat pricing of FEBT, it is possible that patients incur the cost of up to four tablets per episode until a stable dose is found, at which point it is assumed that the prescribing physician changes the patient over to a single tablet corresponding to the effective titrated dose.

5. CADTH COMMON DRUG REVIEW REANALYSES

To account for the limitations identified above, the following analyses were undertaken:

1. Morphine sulfate immediate-release efficacy data applied to comparator

To address the limitation relating to the biased use of MSIR costs and placebo efficacy, CDR made use of efficacy estimates of MSIR available from the manufacturer-commissioned NMA.[3]

2. Patients experience four BTCP episodes per day

Based on available literature sources[12] and input from the clinical experts, CDR's preferred assumption was that patients experienced four episodes of BTCP per day. A range of daily episode frequencies was assessed in sensitivity analyses (Table 13).

3. Length of treatment benefit

Assuming that the length of a BTCP episode was one hour (as in the manufacturer's base case), CDR's preferred assumption was that treatment benefit spanned the length of an episode plus an additional hour (i.e., two hours total). This was based on evidence from one of the pivotal trials[7] that found analgesic efficacy of FEBT at two hours after onset of symptoms.

TABLE 2: CADTH COMMON DRUG REVIEW BASE CASE

Scenario		ICUR ($ per QALY) for FEBT vs. MSIR
	Manufacturer's base case	*$91,592*
1	MSIR efficacy data applied to comparator	$151,860
2	Patients experience 4 episodes of BTCP per day	$205,764
3	Length of treatment benefit spans BTCP episode plus an additional hour (i.e., 2 hours total)	$607,440
1-3	**CDR base case**	**$617,293**

BTCP = breakthrough cancer pain; CDR = CADTH Common Drug Review; FEBT = fentanyl effervescent buccal tablet; ICUR = incremental cost-utility ratio; MSIR = morphine sulfate immediate-release; QALY = quality-adjusted life-year.

At the submitted price, there is a 0% probability of FEBT being cost-effective at both willingness-to-pay thresholds of $50,000 and $100,000 per QALY.

Full details are available in Table 12. As in the manufacturer's base case, results were most sensitive to duration of treatment benefit — in particular, assuming that the benefits of FEBT span only the length of an episode (one hour), the ICUR increases to more than $1.2 million per QALY.

CDR also conducted price reduction analyses (Table 3). In the manufacturer's base case, a price reduction of more than 40% is necessary for the ICUR of FEBT to fall below $50,000 per QALY compared with MSIR (with the caveat that this includes MSIR modelled as having the efficacy of placebo). In CDR's base case, a price reduction of more than 70% is necessary for the ICUR to fall below $100,000 per QALY versus MSIR and a price reduction of 85% ($1.63/tablet) is necessary for the ICUR to fall below $50,000 per QALY.

TABLE 3: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICURs OF FEBT VS. MSIR ($/QALY)		
Price	**Base-Case Analysis Submitted by Manufacturer**	**CDR Base Case**
Submitted ($10.89/episode)	$91,592	$617,293
10% reduction ($9.80/episode)	$81,524	$550,524
15% reduction ($9.26/episode)	$76,490	$517,139
20% reduction ($8.71/episode)	$71,456	$483,754
25% reduction ($8.17/episode)	$66,422	$450,369
30% reduction ($7.62/episode)	$61,389	$416,984
40% reduction ($7.08/episode)	$51,321	$350,214
50% reduction ($6.53/episode)	$41,253	$283,444
60% reduction ($5.99/episode)	$31,185	$216,674
70% reduction ($5.45/episode)	$21,117	$149,904
80% reduction ($2.18/episode)	$11,050	$83,135
90% reduction ($1.09/episode)	$982	$16,365

CDR = CADTH Common Drug Review; FEBT = fentanyl effervescent buccal tablet; ICUR = incremental cost-utility ratio; MSIR = morphine sulfate immediate-release; QALY = quality-adjusted life-year.

6. ISSUES FOR CONSIDERATION

Fentanyl effervescent buccal tablet may not be the optimal therapeutic option for all types of breakthrough cancer pain

As noted by the clinical expert consulted by CDR, and in published literature sources,[13] the treatment and identification of patients with breakthrough pain is difficult, as it is often unclear whether patients are experiencing breakthrough incident or spontaneous pain, or end-of-dose pain related to the inadequate control of baseline pain between doses. End-of-dose pain refers to pain that occurs as the analgesia from the previous dose of background opioid begins to wear off; this may be managed by using the background opioid more frequently or at higher intensity rather than using rescue medication. Further, if episodes of pain are predictable, patients could take a dose of MSIR or other short-acting/IR opioid far enough ahead that the mismatch between the onset of analgesia and the onset of peak pain is avoided. The clinical expert noted that FEBT is likely best used for spontaneous (unpredictable) episodes of BTCP or pain that occurs in response to involuntary actions (e.g., bowel movements, urination). As such, it is unclear that FEBT is the optimal choice for all types of BTCP, and pain specialists might be able to provide effective assistance at lower costs for end-of-dose pain or predictable BTCP.

7. PATIENT INPUT

No patient input was received for this submission.

8. CONCLUSIONS

CDR's reanalysis estimated the ICUR of FEBT versus MSIR to be $617,293 per QALY. There were, however, concerns regarding the external validity of the results from the pivotal trials, which may bias cost-effectiveness estimates — in particular, the trial population likely represented a less severe population with more easily managed pain than would be seen in practice. Given that these patients likely demonstrate more favourable clinical response to FEBT than would be seen in practice, the ICURs produced in both the manufacturer and CDR base cases are possibly underestimates of the true cost-effectiveness of FEBT. In addition, an underestimation of CDR's ICUR is likely, as it does not take into account the potential higher drug cost from titration.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 4 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

TABLE 4: COST COMPARISON OF SHORT-ACTING/IMMEDIATE-RELEASE ANALGESIC OPIOIDS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
Fentanyl Buccal/Sublingual Effervescent Tablets (Fentora)	**100 mcg 200 mcg 300 mcg 400 mcg 600 mcg 800 mcg**	**Sublingual effervescent tablets**	**10.8900 10.8900 10.8900 10.8900 10.8900 10.8900**	**Initiate with 100 mcg, not to exceed 800 mcg; up to 4 episodes per day**	**10.89 to 43.56[a]**
Fentanyl citrate (Abstral)	100 mcg 200 mcg 300 mcg 400 mcg 600 mcg 800 mcg	Sublingual tablets	11.0600[b] 12.4590[b] 14.9410[b] 16.9760[b] 22.6450[b] 28.3030[b]	Initiate with 100 mcg, not to exceed 800 mcg; up to 4 episodes per day	11.06 to 113.21
Fentanyl citrate (Onsolis)	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg	Buccal soluble film	12.000[b] 12.000[b] 12.000[b] 12.000[b] 12.000[b]	Initiate with 200 mcg, not to exceed 1,200 mcg	12.00 to 48.00
Hydromorphone HCl (Dilaudid and generics)	1 mg 2 mg 4 mg 8 mg	tab tab tab tab	0.0959 0.1417 0.2240 0.3528	2 mg to 4 mg every 4 to 6 hours	0.57 to 1.34
	1 mg/mL	liquid	0.0698		0.56 to 1.68
Morphine HCl (M.O.S.)	10 mg 20 mg 40 mg 60 mg	tab tab tab tab	0.1700 0.3243 0.4551 0.5851	10 mg to 30 mg every 4 hours	1.02 to 3.06
Morphine sulfate (MSIR)	5 mg 10 mg 20 mg 30 mg	tab tab tab tab	0.1240[c] 0.1930[c] 0.3440 0.4410	10 mg to 30 mg every 4 hours	1.49 to 2.65
Morphine sulfate (Statex)	5 mg 10 mg 25 mg 50 mg	tab tab tab tab	0.1100 0.1700 0.2250 0.3450	10 mg to 30 mg every 4 hours	1.02 to 3.06
Oxycodone HCl (PMS-Oxycodone, Supeudol)	5 mg 10 mg 20 mg	IR tab	0.1287 0.1896 0.2964	5 mg to 20 mg every 6 hours	0.51 to 1.19
Oxycodone HCl (Oxy-IR)	5 mg 10 mg 20 mg	IR tab	0.2715[d] 0.4010[d] 0.6970[d]	5 mg to 20 mg every 6 hours	1.09 to 2.79

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
Oxycodone HCl & acetaminophen (generics)	5 mg & 325 mg	Tab	0.1285	1 tablet every 6 hours	0.51
Oxycodone HCl & acetylsalicylic acid (generics)	5 mg & 325 mg	Tab	0.3220	1 tablet every 6 hours	1.29
Meperidine HCL/PF (Demerol)	50 mg/mL 75 mg/mL	IM injection	0.8208[e] 0.8424[e]	50 mg to 150 mg every 3 to 4 hours	4.92 to 13.48

HCl = hydrochloride; IM = intramuscular; IR = immediate-release; MSIR = morphine sulfate immediate-release; tab = tablet.
[a] Note that this assumes that the dose has been optimized and does not account for the use of multiple tablets during the titration phase.
[b] QuintilesIMS, Delta PA.[14]
[c] Alberta drug formulary.[15]
[d] Saskatchewan drug formulary.[16]
[e] BC Pharmacare Formulary.[17]
Source: Ontario Drug Benefit Formulary (March 2016).[8]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

The assessment in Table 5 is based on the CADTH Common Drug Review base case.

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS FENTANYL EFFERVESCENT BUCCAL TABLET RELATIVE TO MORPHINE SULFATE IMMEDIATE-RELEASE?

FEBT Vs. MSIR	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	$617,293 per QALY					

CE = cost-effectiveness; FEBT = fentanyl effervescent buccal tablet; MSIR = morphine sulfate immediate-release; NA = not applicable; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 7: AUTHORS' INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review			
☐ Adaptation of global model/Canadian model done by the manufacturer ☐ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☒ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document.	X		
Authors had independent control over the methods and right to publish analysis.			X

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

Fentanyl citrate effervescent tablets have been reviewed by three international health technology assessment (HTA) agencies, namely the Scottish Medicines Consortium (SMC), Pharmaceutical Benefits Advisory Committee (PBAC), and Haute Autorité de Santé (HAS). Table 8 provides the details of the findings of the reviews conducted by SMC and PBAC. The review by HAS came to the decision that "the Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance…"[18] This decision was based on clinical evidence, and health economic evidence was not reviewed. Specifically, efficacy results were assessed based on two randomized controlled trials (RCTs). The results from the two studies showed that the mean pain intensity difference at 30 minutes and 60 minutes following initial pain onset was greater among patients being treated with the fentanyl citrate effervescent tablets than patients receiving placebo. Limitations that restricted the interpretation of efficacy (noted within the clinical evidence) were small cohorts, and the numerous exclusions within the trial. The interpretation of tolerability was noted to be limited due to patients already receiving baseline pain treatment.

TABLE 8: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	SMC (2009)[19]	PBAC (2015)[20]
Treatment	Fentanyl, 100, 200, 400, 600, and 800 mcg buccal tablets	
Price	£5 per dose (100 mcg to 800 mcg)	Price redacted
Similarities with CDR submission	• Cost-utility analysis • Efficacy data were based on indirect comparison	• Efficacy data were based on indirect comparison
Differences with CDR submission	• Comparator: oral transmucosal fentanyl lozenges	• Cost minimization analysis • Fentanyl buccal tablets compared with fentanyl lozenges • Market share was used to estimate the utilization and financial implications of reimbursing fentanyl buccal tablets
Manufacturer's results	If all Scottish patients currently using the lozenge switched to the buccal tablet, there would be cost savings (£123,496) and a QALY increase (0.64) over one year.	Manufacturer results redacted
Issues noted by the review group	• Management of a single 60-minute episode of breakthrough pain was presented as the management of breakthrough pain. It was assumed that episodes were homogenous, and in order to obtain results for the 1-year time horizon, the results for the single episode were simply multiplied by the expected number of episodes per day (4) and the expected number of days of treatment (91). • An indirect comparison was used, as there are no direct comparative studies of FBT and oral transmucosal fentanyl lozenges.	• Dose equivalency between FBT and fentanyl lozenges (100 mg FBT was assumed to be equivalent to 152 mcg fentanyl lozenges). • Market-share approach may be an underestimate of the use of the new fentanyl formulation. The size of the eligible population is uncertain. • Submission did not adequately assess immediate-release opioids as an active comparator.

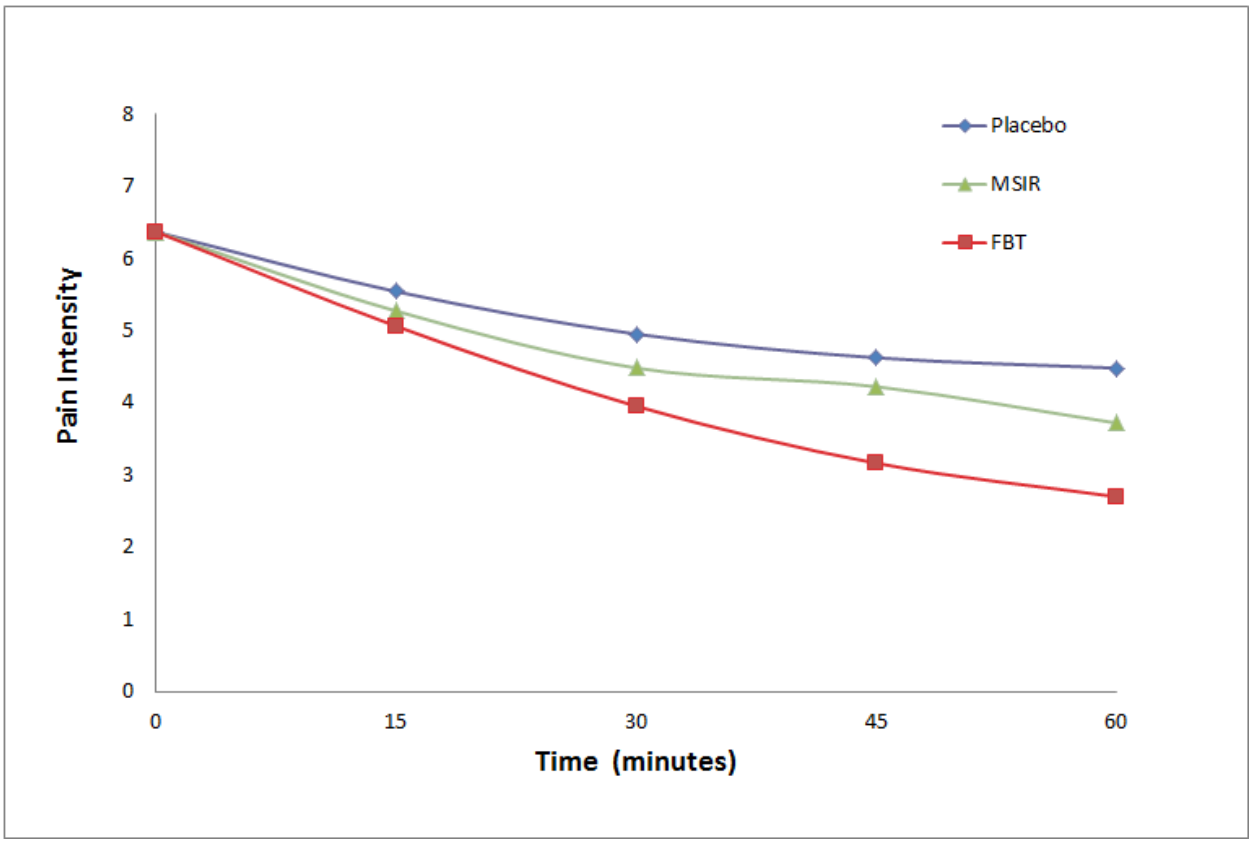
	SMC (2009)[19]	PBAC (2015)[20]
	There were concerns related to the comparability of patients in the different studies and the different doses being used. • A generic measure of quality of life that could be converted into a QALY was not collected in the clinical trials. The manufacturer therefore based the results on a study of patients with chronic back pain.	
Results of reanalyses by the review group (if any)	NA	NA
Recommendation	"Fentanyl buccal tablets are accepted for restricted use within NHS Scotland"	"PBAC did not recommend the listing of fentanyl citrate buccal tablets"

CDR = CADTH Common Drug Review; FBT = fentanyl buccal tablet; NA = not applicable; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life-year.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

FIGURE 1: PAIN INTENSITY CURVES



FBT = fentanyl buccal tablet; MSIR = morphine sulfate immediate-release.
Source: Manufacturer's Pharmacoeconomic Submission.[1]

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	The efficacy of FEBT vs. placebo was established in 2 pivotal phase III double-blind crossover trials.[6,7] Efficacy inputs to the economic model were based on a manufacturer-sponsored NMA consisting of 4 trials comparing FEBT, MSIR, and placebo.[3] The placebo pain intensity profile was based on placebo response in the pooled phase III trials (Study 14[6] and Study 3039[7]). Alternate efficacy values directly comparing FEBT and MSIR were derived from a recent RCT by Mercadante et al.[9]	As noted above, there are concerns regarding the generalizability of results from the trial populations to clinical practice. As noted in the clinical report, [redacted]

Data Input	Description of Data Source	Comment
	Baseline pain intensity curve was based on pain intensities at 15, 30, 45, and 60 minutes from the phase III RCTs.[6,7]	[redacted] Mercadante was not considered, given the use of proportional dosing, which stands in contradiction to the product monograph.[1]
Utilities	Treatment-specific pain intensity profiles were linked to utilities based on a linear regression model. The regression was derived from a study in the UK general population directly eliciting utilities associated with pain intensity profiles using the time-trade-off method conducted to inform an economic evaluation.[11]	Unclear whether appropriate, given that it's not a Canadian cohort. Further, the usual caveats about use of mapped utilities rather than directly measured utilities apply. However, CDR acknowledges a paucity of data in this respect, including failure to collect any quality-of-life data in the phase III trials.
Resource use	Drug use: Dosage of FEBT was not made explicit, but this is inconsequential given the flat pricing across all dosage forms. Impact of treatment on emergency department visits was solicited from experts for the base case. For a sensitivity analysis, impact on emergency department visits, physician visits, and hospitalization were acquired from American literature sources[21] comparing resource use for treated and untreated BTCP.	Appropriate
Adverse events	Not considered, as they were assumed to have a similar side effect profile to other oral opioids.	Unclear whether appropriate
Mortality	Not explicitly considered given the short time horizon. Further, all patients were assumed to be terminally ill.	Seems appropriate
Costs		
Drug	Cost of MSIR was from cost of 20 mg pill taken from ODB formulary. Cost of FEBT was from manufacturer's submitted price.	Appropriate
Administration	Costs of an emergency department visit: Hospital Data Blitz as cited in the manufacturer's economic submission[2]	Appropriate

BTCP = breakthrough cancer pain; CDR = CADTH Common Drug Review; FEBT = fentanyl effervescent buccal tablet; MSIR = morphine sulfate immediate-release; NMA = network meta-analysis; ODB = Ontario Drug Benefit Formulary; RCT = randomized controlled trial.

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
MSIR has equivalent efficacy to placebo.	Inappropriate. Implies that no benefit is derived from taking MSIR. Evidence of the efficacy of MSIR is available, and more appropriate given the Health Canada indication and the population assessed for the efficacy data available. This assumption is hence inappropriate in the context of this submission.
Pain control is linked to resource use.	Appropriate. However, there is a paucity of data on the extent to which pain control can alter resource use.
The daily frequency of BTCP episodes was assumed to be 3 episodes per day.	Possibly an underestimate as per CDR's consulting clinical expert.
Length of the model time horizon.	As FEBT is not strictly indicated for a palliative population, it is possible that some patients may experience BTCP for longer than 6 months, per CDR's consulting clinical expert. This is expected to result in an increased ICUR for FEBT, assuming that the same model structure, inputs, and assumptions can be extended to longer horizons while remaining clinically valid.
Duration of treatment effect: Treatment-specific utilities were assumed to last 24 hours a day rather than during and immediately after the BTCP episode.	Likely inappropriate, although CDR acknowledges a paucity of data in this respect. While some psychological benefit and subjective well-being might be expected with better control of BTCP, the extent to which this affects quality of life is unclear.

BTCP = breakthrough cancer pain; CDR = CADTH Common Drug Review; FEBT = fentanyl effervescent buccal tablet; ICUR = incremental cost-utility ratio; MSIR = morphine sulfate immediate-release.

Manufacturer's Results

TABLE 11: MANUFACTURER'S BASE-CASE RESULTS

	FEBT	Usual Care	Incremental
Cost of drug	$5,930	$185	$5,744
Other health care costs	0	$350	–$350
Total cost	$5,930	$535	$5,394
QALYs	0.22	0.16	0.06
ICUR	$91,592/QALY		

FEBT = fentanyl effervescent buccal tablet; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: Manufacturer's Pharmacoeconomic Submission.[1]

CADTH Common Drug Review reanalyses

TABLE 12: CADTH COMMON DRUG REVIEW BASE CASE — DETAILED RESULTS

	FEBT	MSIR	Incremental
Cost of drug	$7,906	$247	$7,659
Other health care costs	$0	$350	–$350
Total cost	$7,906	$597	$7,309
QALYs	0.31	0.29	0.01
ICUR	$617,293/QALY		

FEBT = fentanyl effervescent buccal tablet; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year.

The following tables present the results of the CADTH Common Drug Review (CDR) sensitivity analyses. Key variables of interest were number of BTCP episodes per day and duration of treatment benefit. A range of daily BTCP episode frequencies were tested — the lower bound of 2 was based on the average daily frequency in Studies 14 and 3039, as reported in the Common Technical Document,[22] and the upper bound of 6 was based on mean values reported in the literature.[12] Duration of treatment benefit was varied between the length of the BTCP episode (one hour) to the manufacturer's base-case assumption of 24 hours.

TABLE 13: CDR SENSITIVITY ANALYSIS — EPISODES PER DAY (INCORPORATING MSIR EFFICACY)

Number of Episodes	ICER
2	$97,956
3 (Manufacturer base case)	$151,860
4 (CDR base case)	**$205,764**
5	$259,669
6	$313,573

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; MSIR = morphine sulfate immediate-release.

TABLE 14: CDR SENSITIVITY ANALYSIS — DURATION OF TREATMENT BENEFIT (INCORPORATING MSIR EFFICACY)

Length	ICER
Only while breakthrough pain occurs	$1,214,881
When breakthrough pain occurs + 1 additional hour (CDR base case)	**$607,440**
When breakthrough pain occurs + 2 additional hours	$404,960
Waking hours (12 hours)	$303,720
24 hours (manufacturer's base case)	$151,860

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; MSIR = morphine sulfate immediate-release.

TABLE 15: CDR MULTI-WAY SENSITIVITY ANALYSIS — EPISODES PER DAY AND DURATION OF TREATMENT BENEFIT (INCORPORATING MSIR EFFICACY)

Number of Episodes	Length of Benefit	ICER
2	Only while breakthrough pain occurs	$1,175,469
	When breakthrough pain occurs + 1 additional hour	$587,735
	When breakthrough pain occurs + 2 additional hours	$391,823
	Waking hours (12 hours)	$195,912
	24 hours (mfr. base case)	$97,956
3	Only while breakthrough pain occurs	$1,214,881
	When breakthrough pain occurs + 1 additional hour	$607,440
	When breakthrough pain occurs + 2 additional hours	$404,960
	Waking hours (12 hours)	$303,720
	24 hours (mfr. base case)	**$151,860**
4	Only while breakthrough pain occurs	$1,234,587
	When breakthrough pain occurs + 1 additional hour (CDR base case)	**$617,293**
	When breakthrough pain occurs + 2 additional hours	$411,529
	Waking hours (12 hours)	$411,529
	24 hours (mfr. base case)	$205,764
5	Only while breakthrough pain occurs	$1,246,410
	When breakthrough pain occurs + 1 additional hour	$623,205
	When breakthrough pain occurs + 2 additional hours	$415,470
	Waking hours (12 hours)	$519,338
	24 hours (mfr. base case)	$259,669
6	Only while breakthrough pain occurs	$1,254,292
	When breakthrough pain occurs + 1 additional hour	$627,146
	When breakthrough pain occurs + 2 additional hours	$418,097
	Waking hours (12 hours)	$627,146
	24 hours (mfr. base case)	$313,573

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; mfr. = manufacturer; MSIR = morphine sulfate immediate-release.

Deterministic sensitivity analyses on CADTH Common Drug Review base case

1. **Utilities** (assuming impact of breakthrough pain on quality of life is less or more than base case by varying slope coefficient in utility regression as done in manufacturer's sensitivity analysis): Range: $545,423 to $763,592
2. **Efficacy values:** Mercadante data[9] (note that Mercadente's use of proportional [rather than titrated] dosing is not in line with the Health Canada indication as stated in the product monograph[1]) and assumption that FEBT is 30% less effective than base line: $228,431 to $1,228,206
3. **Benefit of treatment duration:** As in Table 15, assuming FEBT has efficacy only during the episode, CDR's ICUR rises to $1,234,587. If Fentora is 20% to 30% less effective than baseline, ICURs rise to $1,847,082 to $2,456,413

Probabilistic sensitivity analyses on CADTH Common Drug Review base case

CDR undertook probabilistic sensitivity analyses on its base case. Results are presented for use of both the manufacturer's fixed-effects NMA model (as used in the base case, Table 16) and the random-effects model for treatment efficacy results. Both were based on 5,000 iterations. In both cases, the mean ICUR was more than $1.2 million and there was a 0% probability of FEBT being cost-effective at $50,000 per QALY. Using the fixed-effects model, there was a 0% probability of FEBT being cost-effective at $100,000 per QALY and there was a 15% probability that FEBT was dominated by MSIR (i.e., MSIR cost less and produced more QALYs). Using the random-effects model, there was a 0.5% probability that FEBT would be cost-effective at $100,000 per QALY and a 32% probability that FEBT would be dominated by MSIR.

TABLE 16: CDR PROBABILISTIC SENSITIVITY ANALYSIS — FIXED-EFFECTS MODEL

	FEBT	MSIR	Incremental
Cost of drug	$7,906	$245	$7,661
Other costs	$0	$353	–$353
Total cost	$7,906	$598	$7,308
QALYs	0.27	0.27	0.01
ICER ($ per QALY gained)			**$1,251,057**

CDR = CADTH Common Drug Review; FEBT = fentanyl effervescent buccal tablet; ICER = incremental cost-effectiveness ratio; MSIR = morphine sulfate immediate-release; QALY = quality-adjusted life-year.

Probability of being dominated by MSIR: **14.7%**
Probability of being cost-effective at $50,000/QALY: **0%**
Probability of being cost-effective at $100,000/QALY: **0%**

TABLE 17: CDR PROBABILISTIC SENSITIVITY ANALYSIS — RANDOM-EFFECTS MODEL

	FEBT	MSIR	INCREMENTAL
Cost of drug	$7,906	$244	$7,662
Other costs	$0	$383	–$383
Total cost	$7,906	$627	$7,279
QALYs	0.27	0.27	0.01
ICER ($ per QALY gained)			**$1,301,611**

CDR = CADTH Common Drug Review; FEBT = fentanyl effervescent buccal tablet; ICER = incremental cost-effectiveness ratio; MSIR = morphine sulfate immediate-release; QALY = quality-adjusted life-year.

Probability of being dominated by MSIR: **32.2%**

Probability of being cost-effective at $50,000/QALY: **0%**

Probability of being cost-effective at $100,000/QALY — including all iterations: **0.36%**

Probability of being cost-effective at $100,000/QALY — only non-dominated iterations: **0.53%**

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