Fentanyl Transmucosal Immediate-release Tablets, Film, Nasal Spray, Lozenge and Sublingual Spray

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. The manufacturer's labeling should be consulted for detailed information when prescribing fentanyl transmucosal tablets and buccal soluble film. VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section of the PBM IntraNet .

Executive Summary:

Fentanyl citrate **sublingual tablet** (FSL tablet, ABSTRAL), fentanyl citrate **buccal soluble film** (FB film, ONSOLIS), fentanyl citrate **buccal tablet** (FB tablet, FENTORA), fentanyl pectin **nasal spray** (FPNS, LAZANDA), oral transmucosal fentanyl citrate **lozenge** (OTFC lozenge, ACTIQ) and fentanyl sublingual spray (FSL spray, SUBSYS) are FDA-approved only for the treatment of breakthrough pain in patients with cancer *who are currently receiving and are tolerant to opioid therapy for their underlying persistent cancer pain*. FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray are contraindicated in opioid non-tolerant patients due to the risk of life-threatening respiratory depression. These products should not be substituted for any other fentanyl product.

Transmucosal immediate-release fentanyl (TIRF) products have been shown in short-term, controlled clinical trials to be relatively safe and efficacious in the treatment of breakthrough pain in patients who are currently on opioid therapy for persistent cancer-related pain. Potential advantages of FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray over other oral opioids include avoidance of first-pass metabolism, moderately faster onset of action, and an alternative method of administration in patients with dysphagia, nausea, or vomiting. Additional rescue medications may still be necessary if breakthrough pain is not relieved by the fentanyl product, as the number of doses allowed per episode and per day are limited, with FB film and FPNS allowing only one dose per episode (as compared with 2 doses for the other formulations).[1,2]

There have been no direct efficacy and safety comparisons among the different TIRF formulations available in the U.S. In a direct comparison with oral immediate-release (OIR) morphine, FPNS achieved a greater magnitude of pain reduction that was statistically significant but of questionable clinical importance, and reached a clinically meaningful pain reduction (PID $\geq$ 2) less than 5 minutes earlier than OIR morphine. In indirect comparisons, FPNS and OIR morphine seemed to achieve PID $\geq$ 2 faster than FB tablet, OTFC lozenge, and OIR oxycodone (by at least 20 minutes for each).

FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray doses must be individually titrated and are not interchangeable. If a TIRF product is considered for addition to the VA National Formulary, it may be wise to add only one TIRF product to reduce the potential for inappropriate conversions between different TIRF products, and to restrict its use to patients who are opioid-tolerant, have severe, recurrent, *unpredictable* cancer-related breakthrough pain (CBTP), and are unable to take or tolerate OIR morphine. Providers should be educated that, in contrast to immediate-release rescue opioids, the dose of TIRF products must be titrated rather than calculated as a percentage of the around-the-clock opioid dose.

Because FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray are not dose equivalent with other opioids, specific dose titration guidelines must be followed when initiating these drugs to reduce the risk of respiratory depression, and close follow-up may be necessary during initiation.[1,2] This titration requirement may

make the use of these products difficult for some outpatients. The possibility of patients having to use multiple units during the titration phase may be complicated and time consuming.

The value of these products in the inpatient setting is limited due to the involved titration process and lack of proven benefit over IV morphine, which is easily dosed and administered but requires intravenous access.

As of March 12, 2012, providers, pharmacies, and patients must be enrolled in the shared Transmucosal Immediate-release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program, to prescribe, dispense, and receive TIRF products. This REMS program may help to mitigate misuse, abuse, addiction, and diversion of TIRF products, but the fast-on, fast-off properties of these agents still make them highly desirable drugs of abuse. The potential risks and benefits of TIRF products need to be carefully weighed on an individualized basis. TIRF therapy will require diligent opioid risk assessment and monitoring as part of a comprehensive, multidisciplinary approach to pain management in patients with CBTP.

Introduction

Breakthrough pain (BTP) has been defined as "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain."[1] The painful episodes are typically rapid in onset, severe in intensity, and relatively short (about 30 minutes) in duration.

The standard of care for cancer-related breakthrough pain (CBTP) has been immediate-release (IR) oral short-acting opioids, which have been observed to produce a delayed onset (20 to 30 minutes; peak 30 to 60 minutes)[1] that often occurs after the episode of BTP has ended. Their effects also last longer (2 to 4 hour) than the average duration of BTP episodes. A task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland suggest that IR oral short-acting opioids may have a role in the treatment of predictable CBTP when the medication can be taken about 30 to 60 minutes before the BTP trigger.[1] Their characteristics, however, do not parallel the usual temporal course of breakthrough episodes of pain (i.e., rapid onset within minutes, average duration of 30 minutes),[2] and these limitations led to the development of transmucosal immediate-release fentanyl (TIRF) products.

Until recently, there were two FDA-approved products for CBTP: oral transmucosal fentanyl citrate lozenge ("OTFC lozenge", ACTIQ by Cephalon, approved in 1998, and generics by Barr and Mallinkrodt) and fentanyl citrate buccal tablet ("FB tablet," FENTORA by Cephalon, 2006, and generic by Watson Labs). Four additional products have been approved by the FDA: fentanyl citrate buccal soluble film ("FB film", ONSOLIS by Meda Pharmaceuticals, 2009), fentanyl [citrate] sublingual tablet ("FSL tablet," ABSTRAL by Prostrakan, Inc., 2011[a]), fentanyl pectin nasal spray (FPNS, LAZANDA, by Archimedes Pharma US, Inc., 2011), and fentanyl sublingual spray ("FSL spray," SUBSYS by Insys Therapeutics, Inc., 2012).

The purposes of this review are to (1) evaluate the available evidence of comparative safety, tolerability, efficacy (in controlled clinical trials), effectiveness (in naturalistic studies), cost, and other pharmaceutical issues that would be relevant to evaluating each of the transmucosal IR fentanyl (TIRF) formulations for possible addition to the VA National Formulary; (2) define their roles in therapy; and (3) identify parameters for their rational use in the VA.

[a] FSL tablet was developed using the technology of a SL fentanyl tablet by Orexo AB (Sweden), a company that partners with ProStrakan.

Pharmacology/Pharmacokinetics

Absorption

The absorption of fentanyl from FB film, FB tablet, and OTFC lozenge is a combination of rapid absorption through the buccal mucosa (~50% for FB film and FB tablet; ~25% for OTFC lozenge), followed by a more delayed absorption of swallowed fentanyl through the gastrointestinal tract (~50% FB film and tablet; ~75% OTFC lozenge). The amount of fentanyl absorbed from FSL spray through the buccal mucosa vs. GI tract varies due to differences in user administration.

FSL tablet is absorbed mainly through the oral mucosa.[3]

FPNS uses a pectin-based drug delivery system, PecSys, which is designed to produce a rapid, controlled absorption. FPNS is absorbed through the nasal mucosa.[4] Median T_{max} values range from 15-21 minutes after administration of a single dose.

Table 1. Pharmacokinetics[Error! Bookmark not defined.–4]

	Cmax (ng/mL)	AUC_{inf} (hr.ng/mL)
FB FILM		
200 mcg	0.38 ± 0.07	3.46 ± 0.72
600 mcg	1.16 ± 0.19	11.72 ± 5.29
1200 mcg	2.19 ± 0.54	20.43 ± 4.52
FSL TABLET		
100 mcg	0.187 ±0.33	0.974 ± 0.34
200 mcg	0.302 ± 0.31	1.92 ± 0.27
400 mcg	0.765 ± 0.38	5.49 ± 0.35
800 mcg	1.42 ± 0.33	8.95 ± 0.33
FB TABLET		
100 mcg	0.25 ± 0.14	0.98 ± 0.37
200 mcg	0.40 ± 0.18	2.11 ± 1.13
400 mcg	0.97 ± 0.53	4.72 ± 1.95
800 mcg	1.59 ± 0.90	9.05 ± 3.72
FPNS		
100 mcg	0.3515	2.4605
200 mcg	0.7808	4.3599
400 mcg	1.5521	7.5134
800 mcg	2.8440	17.272
OTFC LOZENGE		**AUC_{1-1440} (ng/mL minute)**
200 mcg	0.39	102
400 mcg	0.75	243
800 mcg	1.55	573
1600 mcg	2.51	1026
FSL SPRAY		
400 mcg	0.813	5.761

Metabolism

Fentanyl is metabolized in the liver and intestinal mucosa by CYP3A4. First-pass metabolism is lessened by the buccal, sublingual, nasal, or transmucosal administration routes of FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray.[**Error! Bookmark not defined.**–4]

FDA Approved Indication(s) and Off-label Uses

FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray are FDA-approved only for the management of breakthrough pain in cancer patients, 18 years of age and older, *who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.*

Patients are considered to be opioid tolerant if they are taking at least oral morphine 60 mg / day, transdermal fentanyl 25 mcg / hour, oral oxycodone 30 mg / day, oral hydromorphone 8 mg / day, or an equianalgesic dose of another opioid for one week or longer.

Potential off-label use includes treatment of noncancer BTP. This off-label use is somewhat supported by two multicenter, double-blind, randomized placebo-controlled trials that have shown FB tablet to be efficacious in relieving BTP in patients with chronic low back pain[5] and neuropathic pain[6] during short-term (3-week) therapy. A systematic review by Chou, et al. (2009) recommended: "In patients on around-the-clock [chronic opioid therapy] with breakthrough pain, clinicians may consider as-needed opioids based upon an initial and ongoing analysis of therapeutic benefit versus risk (weak recommendation, low-quality evidence)."[7] There was insufficient evidence to recommend guidance on optimal treatment approaches for noncancer BTP, and additional studies were needed to evaluate the long-term harms and benefits and to compare different short-acting or rapid-onset opioids.

Current VA National Formulary Alternatives

There are no rapid-onset transmucosal opioid products on VANF. In the outpatient setting, the standard treatment for any type of CBTP (spontaneous, predictable, or unpredictable) has been immediate-release (IR), short-acting oral opioids. However, a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland consider them suboptimal for spontaneous and unpredictable CBTP and more appropriate for prophylactic analgesia of predictable CBTP or for CBTP lasting longer than 60 minutes.[1] IR opioids on VANF are listed below.

- Acetaminophen/Hydrocodone LIQUID,ORAL and TAB
- Acetaminophen/Oxycodone CAP,ORAL, LIQUID, ORAL, and TAB
- Codeine/Acetaminophen ELIXIR and TAB
- Hydromorphone TAB
- Morphine CAP,IR, LIQUID,ORAL, TAB,IR
- Oxycodone LIQUID,ORAL and TAB

Dosage and Administration

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FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray are NOT equivalent on a mcg-per-mcg basis to any other fentanyl products. Dose titration must be performed according to the manufacturers' recommendations for all patients starting these medications.[Error! Bookmark not defined.–4] **Refer to Product Information for complete prescribing recommendations.**

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When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl product to FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge or FSL spray. Patients beginning treatment with FSL tablet, FPNS and FSL spray must begin with titration from the 100 mcg dose. For FB film, FB tablet, and OTFC lozenge, the initial dose from which to begin titration is 200 mcg.

When dispensing, do not substitute an FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge or FSL spray prescription for other fentanyl products. Differences exist in the pharmacokinetics of these products compared to each other and other fentanyl products that could result in clinically important differences in the amount of fentanyl absorbed and could result in fatal overdose.

FSL Tablet Dosage and Administration[3]

FSL Tablet Dose Titration

- Start titration of ALL patients with an initial dose of 100 mcg.
- If adequate analgesia is achieved within 30 minutes, continue treating at this dose.
- If adequate analgesia is not achieved within 30 minutes, patients may use a second dose of equal strength. No more than two doses may be used to treat a single episode. Patients must wait at least two hours before treating another episode with FSL tablet.
- If pain is not relieved at that dose, titrate dose according to the table below.

Table 2. Recommended FSL Tablet Dosage Unit Combinations and Dose titration

Dose	Unit Combination(s)				
100 mcg	1 x 100 mcg tablet				
200 mcg	2 x 100 mcg tablets	or	1 x 200 mcg tablet		
300 mcg	3 x 100 mcg tablets	or	1 x 300 mcg tablet		
400 mcg	4 x 100 mcg tablets	or	2 x 200 mcg tablets	or	1 x 400 mcg tablet
600 mcg	3 x 200 mcg tablets	or	1 x 600 mcg tablet		
800 mcg	4 x 200 mcg tablets	or	1 x 800 mcg tablet		

**Patients should use no more than 4 tablets of any strength(s) of FSL tablet at one time.

FSL Tablet Maintenance

- If the maintenance dose becomes no longer effective, increase the dose as directed in the Dose Titration section
- *FSL tablet should be limited to four doses per day.*

FSL Tablet Administration

Immediately after removing tablet(s) from blister unit, place on floor of the mouth directly under the tongue. Do not chew, suck, or swallow FSL tablets. Allow tablet(s) to dissolve completely before eating or drinking. Mouth may be moistened with water prior to administration in patients with dry mouth.

FSL Tablet Discontinuation

For patients discontinuing all opioid therapy, consider discontinuing FSL tablet along with tapering other opioids to reduce the risk of withdrawal symptoms. If patients are to continue chronic opioid therapy but no longer need treatment for breakthrough pain, FSL tablets can generally be discontinued immediately.

FB Film Dosage and Administration[Error! Bookmark not defined.]

FB Film Dose Titration

- Start ALL patients with an initial dose of one 200-mcg film.
- If adequate pain relief is achieved with 200 mcg, continue treating at this dose.

- If adequate pain relief is not achieved, increase the dose used in each subsequent episode using the schedule below until reaching a dose that provides adequate pain relief.

Table 1 Recommended FB Film Dosage Unit Combinations (Max. 4 Films at One Time)

Dose	Unit Combination
200 mcg	1 x 200 mcg film
400 mcg	2 x 200 mcg film
600 mcg	3 x 200 mcg film
800 mcg	4 x 200 mcg film
1200 mcg	1 x 1200 mcg film

- No more than four FB film dosage units should be used simultaneously and films should not be placed on top of one another

- *Only one dose of FB film should be used to treat each episode of breakthrough pain (FB film should not be redosed within an episode).* If adequate analgesia is not achieved within 30 minutes of treatment with FB film, a rescue medication may be used as directed by a healthcare provider.

- Doses of FB film should be separated by at least 2 hours

FB Film Maintenance

- If the maintenance dose becomes no longer effective, increase the dose as directed in the Dose Titration.

- *FB film should be limited to four doses per day.*

FB Film Administration

- Do not tear or cut FB film.

- Use tongue or rinse mouth with water to wet an area for placement of FB film.

- Open package immediately prior to use and place the entire FB film near the tip of a dry finger with the pink side facing up.

- Place the pink side of the film against the inside of the cheek; press and hold in place for 5 seconds.

- Liquids may be consumed after 5 minutes.

- The FB film will dissolve within 15 to 30 minutes after application.

- The film should not be manipulated with the tongue or fingers, and eating food should be avoided until the film has dissolved.

FB Tablet Dosage and Administration[Error! Bookmark not defined.]

FB Tablet Dose Titration

- The initial dose of FB tablet is 100 mcg for ALL patients, with the only exception being patients already using OTFC lozenge at a dose of 600 mcg or greater.
- There are no conversion recommendations to FB tablet from any fentanyl product other than OTFC lozenge (ACTIQ).
- When converting patients from OTFC lozenge, use the table below. These are recommended starting doses of FB tablet and are not equianalgesic to OTFC lozenge doses.

Table 2 Conversion from OTFC Lozenge to FB Tablet

OTFC Lozenge Dose (mcg)*	Initial FB tablet dose (mcg)
200	100 mcg tablet
400	100 mcg tablet
600	200 mcg tablet
800	200 mcg tablet
1200	2 x 200 mcg tablets
1600	2 x 200 mcg tablets

* ACTIQ is the OTFC lozenge product specified in the FENTORA Product Information

- For patients not currently using OTFC lozenge, initial dose is 100 mcg.
- If adequate analgesia is not achieved with 100 mcg, titrate using increments of 100 mcg up to 400mcg. For doses above 400 mcg (600 mcg or 800 mcg), titrate using multiples of 200 mcg.
- No more than four FB tablet dosage units should be used simultaneously.
- If adequate analgesia is not achieved within 30 minutes, patients may use one additional dose using the same strength for that episode. No more than two doses of FB tablet may be used per episode.

FB Tablet Maintenance

- Once titrated to an effective dose, patients should use only one FB tablet of the appropriate strength per episode.
- *Patients must wait at least four hours between treatments with FB tablet*

FB Tablet Administration

- Remove tablet from blister unit immediately prior to administration by peeling back the blister unit to expose the tablet. Do not push the tablet through the blister as this may cause damage to the tablet.
- Once removed from blister, immediately the entire tablet in the buccal cavity. Do not split FB tablets.
- Leave the tablet in the buccal cavity until disintegrated, about 14-25 minutes. Do not suck, chew, or swallow tablet.

- If remnants of FB tablet remain after 30 minutes, swallow with a glass of water.
- It is recommended that patients alternate sides of the mouth when using subsequent doses of FB tablet.

FPNS Dosage and Administration[4]

FPNS Dose Titration

- Starting dose for ALL patients is ONE 100 mcg spray.
- If adequate analgesia is achieved within 30 minutes, continue treating at this dose.
- If adequate analgesia is not achieved, titrate dose according to the table below.
- *Only one dose of FPNS should be used to treat each episode of breakthrough pain (FPNS should not be redosed within an episode).*
- Doses of FPNS should be separated by at least 2 hours.

Table 3 Recommended FPNS Dosage Unit Combinations and Dose Titration

Dose	Unit Combination
100 mcg	1 x 100 mcg spray
200 mcg	2 x 100 mcg spray (1 in each nostril)
400 mcg	1 x 400 mcg spray
800 mcg	2 x 400 mcg spray (1 in each nostril)

FPNS Dose Maintenance

- No more than four doses of FPNS should be used per day and doses must be separated by at least 2 hours.
- If adequate analgesia is not achieved 30 minutes after administration of FPNS, or if another episode occurs within 2 hours after a dose of FPNS, patients may use a rescue medication as directed by their provider.

FPNS Dose Administration

- Prime the device before use by spraying 4 times into the pouch.
- Insert nozzle a short distance (~1/2 inch or 1 cm) into nostril and point toward bridge of nose, tilting bottle slighty.
- Press down firmly on finger grips until a “click” is heard and the number in the counting window advances by one.
- *Patients should be advised that the fine mist spray is not always felt; patients should rely on the audible click and advancement of dose counter to confirm a dose has been administered.*

FPNS Discontinuation

For patients discontinuing all opioid therapy, consider discontinuing FPNS along with tapering other opioids to reduce the risk of withdrawal symptoms. If patients are to continue chronic opioid therapy but no longer need treatment for breakthrough pain, FPNS
can generally be discontinued immediately.

OTFC Lozenge Dosage and Administration[Error! Bookmark not defined.]

OTFC Lozenge Dose Titration

- The initial dose for ALL patients is 200µg. OTFC lozenge should be consumed over 15 minutes
- If adequate analgesia is not achieved 15 minutes after completion of lozenge (30 minutes after start of lozenge), patients may take one additional dose for that BTP episode.
- Patients must wait at least 4 hours before treating another episode with OTFC lozenge.
- The 200µg dose should be tried for several episodes of BTP before titrating upward.
- If adequate analgesia is not achieved, increase to the next available dose.
- OTFC lozenge doses include 200, 400, 600, 800, 1200, and 1600µg.

OTFC Lozenge Dose Maintenance

- Once an effective dose is found, patients generally use only ONE lozenge per episode. If adequate analgesia is not achieved, one additional lozenge may be used on these occasions.
- Patients must wait at least 4 hours before treating another episode with OTFC lozenge.
- No more than four units should be used per day.

OTFC Lozenge Administration

- Open OTFC lozenge blister package immediately prior to use.
- Place lozenge between cheek and lower gum, occasionally moving lozenge from one side to the other using the handle.
- OTFC lozenge should be sucked, NOT chewed.
- Consume lozenge over a 15-minute period.
- Swallowing OTFC lozenge may result in lower peak concentrations and bioavailability than when consumed as directed.

FSL Spray Dosage and Administration

FSL Spray Dose Titration

- FSL spray is available in 100µg, 200µg, 400µg, 600µg, and 800µg strengths.
- To reduce the risk of overdose during titration, prescribe only one strength of FSL spray at any time and limit the number of units available in the home (e.g., prescribe only an initial titration supply of FSL spray units).

- The initial dose of FSL spray is always 100 mcg with the only exception being patients already using OTFC lozenge.

Patients on OTFC Lozenge

- For patients being converted from OTFC lozenge, prescribers must use the Initial Dosing Recommendations for Patients on OTFC lozenge table below (Table 4). Patients must be instructed to stop the use of OTFC lozenge and dispose of any remaining units.

Table 4 Initial Dosing Recommendations for Patients on OTFC Lozenge

Current OTFC Lozenge Dose	Initial FSL Spray Dose
200 mcg	100 mcg
400 mcg	100 mcg
600 mcg	200 mcg
800 mcg	200 mcg
1200 mcg	400 mcg
1600 mcg	400 mcg

- For patients converting from **OTFC lozenge doses 400 mcg and below,** titration should be initiated with 100 mcg FSL spray and should proceed using multiples of this strength.

- For patients converting from **OTFC lozenge doses of 600 and 800 mcg,** titration should be initiated with 200 mcg FSL spray and should proceed using multiples of this strength.

- For patients converting from **OTFC lozenge doses of 1200 and 1600 mcg,** titration should be initiated with 400 mcg FSL spray and should proceed using multiples of this strength.

All Other Patients

- The initial dose of FSL spray to treat episodes of breakthrough cancer pain is **always** 100 mcg.

- If adequate analgesia is not achieved within 30 minutes, patients may take ONLY ONE additional dose of the same strength for that BTP episode (maximum of two doses per BTP episode).

- Treatment with FSL spray for each BTP episode must be separated by at least 4 hours.

- If adequate analgesia is not achieved with one dose after several trials, increase to the next available dose according to the table below.

Table 5 Recommended FSL Spray Dosage Unit Combinations and Dose Titration

Dose	Unit Combination
100 mcg	1 x 100 mcg
200 mcg	1 x 200 mcg
400 mcg	1 x 400 mcg
600 mcg	1 x 600 mcg
800 mcg	1 x 800 mcg
1200 mcg	2 x 600 mcg
1600 mcg	2 x 800 mcg

FSL Spray Dose Maintenance

- Once an effective dose is found, patients should generally use only ONE dose / spray per episode. If adequate analgesia is not achieved within 30 minutes of a dose, only one additional spray may be used on these occasions.
- Patients must wait at least 4 hours before treating another BTP episode.
- No more than 4 BTP episodes should be treated with FSL spray per day.

FSL Spray Administration

- Remove FSL spray from blister pack immediately prior to use.
- Swallow any saliva in mouth.
- Hold spray unit upright.
- Point the nozzle into your mouth, under your tongue.
- Squeeze fingers together to spray under the tongue.
- Hold medication under the tongue for 30-60 seconds. Do not spit out medicine or rinse mouth.

FSL Spray Storage and Disposal

Child Safety Kits containing an interim storage bag, bag lock, cabinet and drawer child safety latches are available from Insys Therapeutics, Inc.

The spray unit will remain locked after use. Each prescription of FSL spray includes disposal bags. All used units should be sealed in a disposal bag and can be discarded in regular trash. Any unused spray units should be emptied in the provided disposal bottle, which should be sealed and placed in a disposal bag, then the bag may be discarded in regular trash.

FSL Spray and Oral Mucositis

In cancer patients with Grade 1 mucositis who were treated with FSL spray, Cmax and overall drug exposure were increased. Monitor patient closely for respiratory and central nervous system depression, particularly during initiation of therapy.

For patients with Grade 2 mucositis or higher, avoid use of FSL spray unless the benefits outweigh the potential risk of respiratory depression from increased exposure.

Table 6 Dosage and Administration – All Transmucosal Immediate-release Fentanyl Products

Transmucosal Fentanyl Product	Initial Dose	Doses allowed per episode	Minimum time between treatments	Max. doses per day	Max. dosage units per dose
FSL tablet (ABSTRAL)	100 mcg	2 (30 min apart)	2 hours	4	4
FB film (ONSOLIS)	200 mcg	1 (No redosing)	2 hours	4	4
FB tablet (FENTORA)	100 mcg*	2 (30 min apart)	4 hours	Not indicated	4
FPNS (LAZANDA)	100 mcg	1 (No redosing)	2 hours	4	2 sprays**
OTFC lozenge (ACTIQ)	200 mcg	2 (30 min apart)	4 hours	4	1
FSL spray (SUBSYS)	100 mcg*	2 (30 min apart)	4 hours	4	2

Sources: Product Information for ONSOLIS, ABSTRAL, FENTORA, LAZANDA, SUBSYS, and ACTIQ[Error! Bookmark not defined.–4]
* Or as recommended if using OTFC lozenge. ** 1 spray in each nostril.

Efficacy

Efficacy Measures

Studies are limited by the lack of an accepted definition, standardized classification system and fully validated assessment tool for CBTP.[8]

Pain Intensity (PI): Pain intensity measured on an 11-point numerical rating scale (0-no pain; 10-worst pain). One trial used a 100-mm visual analogue scale (VAS).[12]
Pain Intensity Difference (PID): The change (reduction) in PI from baseline to the assessment time point. Two trials did not report PID.[1,18]
Summed Pain Intensity Difference (SPID): The sum of PID over a given interval (e.g., SPID60 refers to the sum of PID over 60 minutes).
Pain Relief (PR): Degree of pain relief as measured on a 5-point verbal rating scale (0-no relief; 4-complete relief).
Clinically Meaningful Pain Relief (CMPR): Reduction in pain from baseline (PID) of ≥ 2 points or ≥ 33% on an 11-point numerical rating scale.
Patient Satisfaction: Rated on a 5-point verbal rating scale ((poor, fair, good, very good, and excellent).

The Minimal Clinically Important Differences (MCIDs; i.e., minimal clinically important changes in pain scales from baseline) have been derived using data from placebo-controlled trials in patients who treated CBTP with OTFC lozenge (Table 7)[9,10]

Table 7 Minimal Clinically Important Differences to Yield Adequate Pain Relief in Cancer-related Breakthrough Pain

Pain Scale	Description	MCID
PID	Absolute pain intensity difference, 0–10 scale	2
PR	Pain relief, 0 (None) to 4 (Complete)	2 (Moderate)
SPID60	Sum of pain intensity difference over 60 min	2
%PID	Percentage pain intensity difference, 0–100% scale	33%
% Max TOTPAR60	Percentage of maximum total pain relief over 60 min	33%
GMP	Global medication performance, 0 (Poor) to 4 (Excellent)	2 (Good)

Source: Farrar (2000),[9] Farrar (2003)[10]

Summary of Clinical Trials

A total of 12 controlled trials evaluated TIRF formulations in the treatment of CBTP and 2 observational studies evaluated their safety (Table 8). Only one study evaluated the long-term (≥ 12 months) durability of effects.[16]

Dose-controlled trials were excluded. Indirect comparisons were limited by variability in outcome measures and observation time points among the trials.

Table 8 Summary of Controlled Clinical Trials Evaluating TIRF in CBTP

Product	Reference	Design	N
FSL TABLET	Rauck (2009)[11]	MC PC Phase III RCT	N = 131 Efficacy = 61 Safety = 72
	Lennernäs (2010)[12]	MC DB CO Phase II RCT	Efficacy Per protocol = 23 Efficacy ITT = 27 Safety = 38
FB FILM	Rauck (2010)[13]	MC DB PC CO RCT	Efficacy ITT = 80 Safety = 151
FB TABLET	Portenoy (2006)[14]	MC DB PC RCT	Efficacy = 68 Safety = 123
	Slatkin (2007)[15]	MC DB PC RCT	Efficacy = 78 Safety = 125
	Weinstein (2009)[16]	Long-term (≥ 12 mo), OL MC extension study	Overall safety = 232 Titration safety = 112 Maintenance safety N = 197
	Ashburn (2011)[30]	MC DB DD CO RCT (vs. oral IR oxycodone)	Efficacy = 183 Safety = 320
FPNS	Portenoy (2010)[17]	MC DB PC CO RCT	Efficacy ITT = 73 Safety = 113
	Taylor (2010)[18]	MC DB PC CO RCT	Efficacy ITT = 76 Safety = 113
	Portenoy (2010)[19]	16-week MC OL	Safety = 403
	Fallon (2011)[24] Davies (2011)[25]	MC DB DD CO RCT (vs. oral IR morphine)	Efficacy = 84 Safety = 106
OTFC LOZENGE	Farrar (1998)[20]	MC DB PC CO RCT	Efficacy ITT = 86
	Mercadante (2007)[21]	OL CO RCT (vs. i.v. morphine)	Efficacy = 25
	Coluzzi (2001)[Error! Bookmark not defined.]	MC DB DD CO RCT (vs. oral IR morphine)	Efficacy mITT = 75 Safety = 134
	Mercadante (2009)[23]	OL CO RCT (vs. INFS [INSTANYL])	Efficacy ITT = 139 Safety = 139
FSL SPRAY	Rauck (2012)[22] (INS-05-001)	MC DB PC CO RCT	Efficacy ITT = 96 Safety = 130

Table 9 PID in Head-to-Head Open-label RCT

	INSTANYL® INFS		OTFC Lozenge	
	Mean	SE	Mean	SE
5 min				
SR by Vissers 2010	NPT		NPT	
Mercadante 2009	1.1*	NR	0.5	NR
10 min				
SR by Vissers 2010	2.39*	0.19	1.10	0.11
Mercadante 2009	2.25*	NR	1.1	NR
15 min				
SR by Vissers 2010	3.39*	0.20	1.96	0.15
Mercadante 2009	3.2*	NR	1.8	NR
20 min				
SR by Vissers 2010	4.06*	0.21	2.78	0.17
Mercadante 2009	3.7*	NR	2.5	NR
30 min				
SR by Vissers 2010	4.54*	0.20	3.69	0.19

Mercadante 2009	4.1*	NR	3.4	NR
60 min				
SR by Vissers 2010	4.98*	0.20	4.73	0.18
Mercadante 2009	4.5*	NR	4.4	NR

Results shown are those for the study by Mercadante (2009)[23] as reported in a systematic review by Vissers (2010)[32] and in the original article (as least squared mean PID).
NPT, Not a protocolled time point; SR, Systematic review
* $p < 0.05$

Head-to-Head Trials

There were no head-to-head trials between TIRF products marketed in the U.S. One open-label, randomized trial that was sponsored by Nycomed, the manufacturer of INSTANYL®, an intranasal fentanyl spray (INFS) marketed in Europe, directly compared INSTANYL and OTFC lozenge in terms of efficacy and safety.[23] INSTANYL was superior ($p < 0.05$) to OTFC lozenge at each time point (5, 10, 15, 20, 30, and 60 minutes) in terms of adjusted least squared mean PID. The onset of the first clinically meaningful PID (decrease of ≥ 2 points on an 11-point numerical rating scale from baseline) was at 10 minutes for INSTANYL and at 15 to 20 minutes for OTFC lozenge. Results of this study as reported in a systematic review[32] that was also funded by Nycomed and as reported in the original article are shown in Table 9. The results reported in the systematic review were somewhat higher than those reported for the same study in the original article.

Active-controlled Trials

Three trials compared a TIRF formulation with an oral IR opioid (Table 10)[**Error! Bookmark not defined.**,30,24] and one trial compared OTFC lozenge with intravenous morphine.[21] In the oral IR opioid trials, a clinically meaningful PID (reduction in pain intensity by ≥ 2 points from baseline) was reached at 10 minutes with FPNS (1 RCT), at 15 and 30 minutes with oral immediate-release (OIR) morphine (2 RCTs), at 30 minutes with OTFC lozenge (1 RCT), and at 45 minutes with FB tablet (1 RCT) and with OIR oxycodone (1 RCT) (Table 10). The percentage of patients achieving CMPR at 15 minutes showed statistically significant treatment differences ($p < 0.05$) in the three active-controlled trials: 75.5% for FPNS versus 69.3% for OIR morphine (calculated difference, 6.2%; $p < 0.05$),[24] 42.3% for OTFC lozenges versus 31.8% for OIR morphine (calculated difference, 10.5; $p < 0.05$),[26] and 13.0% for FB tablet versus 9% for OIR oxycodone (calculated difference, 4; reported 95% CI for treatment difference 1.0–2.0).[30] The greatest reduction in PI occurred with FPNS (PID of 5.40 at 60 minutes) and OIR morphine (PID of 4.90 at 60 minutes).

A multicenter, double-blind, double-dummy, multiple crossover randomized trial that directly compared FPNS with oral immediate-release morphine sulfate in 84 patients with CBTP showed superiority of the nasal formulation in terms of PID beginning at 10 minutes and in the percentages of episodes showing clinically meaningful pain relief (≥ 2-point reduction in PI) beginning at 15 minutes.[25,24] However, the effect size in terms of the percentage of episodes with total pain relief ≥ 33% was moderate, with an NeNT of 16 at 15 minutes.

Three systematic reviews have compared TIRF products with MOR IR. A Cochrane review in 2007 included one RCT (N = 134)[26] that showed OTFC lozenge was superior to MOR IR in the on-demand treatment of CBTP. The review concluded that there is limited evidence that transmucosal fentanyl produces faster CBTP relief than morphine.[27] Another Cochrane review (last edited in 2009) also found only the one trial[**Error! Bookmark not defined.**] that compared OTFC lozenge with MOR IR (three others compared OTFC lozenge with placebo).[28] More recently (2010), the results of a systematic review showed that MOR IR is ineffective for the first 45 minutes and led the authors to conclude that MOR IR is not a suitable agent for treatment of CBTP.[29]

Table 10 PID in DB Active-controlled RCTs (11-point NRS; ITT or FAS Analyses)

	FB Tab		FPNS		OTFC Lozenge		OIR MOR		OIR OXY	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
5 min										
Ashburn 2011	0.13*	DE							0.08	DE
Fallon 2011			1.0	DE			1.0	DE		
10 min										
Ashburn 2011	0.3*	DE							0.2	DE
Fallon 2011			2.00	DE			1.80	DE		
15 min										
Ashburn 2011	0.8*	0.18							0.6	0.15
Fallon 2011			3.02*	0.21			2.69	0.18		
Coluzzi 2001					1.86*	0.19	1.44	0.14		
30 min										
Ashburn 2011	1.9*	0.25							1.6	0.18
Fallon 2011			4.10*	DE			3.70	DE		
Coluzzi 2001					2.88*	0.19	2.39	0.15		
45 min										
Ashburn 2011	2.81*	0.26							2.6	0.2
Fallon 2011			4.80*	DE			4.20	DE		
Coluzzi 2001					3.52*	0.19	3.03	0.17		
60 min										
Ashburn 2011	3.3*	DE							3.2	DE
Fallon 2011			5.40*	DE			4.90	DE		
Coluzzi 2001					4.02*	0.23	3.52	0.16		

MOR, Morphine; OIR, Oral immediate-release; OXY, Oxycodone
DB, Double; DE, Difficult to estimate from report;FAS, Full analysis set; ITT, Intent-to-treat; NR, Not reported; NRS, Numerical rating scale; PID, Pain intensity difference (observation point – baseline); RCT, Randomized clinical trial
* Indicates $p < 0.05$ for fentanyl TM IR formulation vs. comparator

One double-blind crossover RCT (N = 323 enrolled, 320 analyzed for safety, 183 analyzed for efficacy) compared FB tablets with OIR oxycodone in patients with BTP associated with cancer or noncancer chronic pain.[30] Mean pain intensity difference (i.e., change from baseline using an 11-point numerical rating scale) was assessed at 15 minutes (PID15, primary efficacy variable) and 30 minutes (PID30). The mean (SD) PID15 was 0.82 (1.12) for FB tablets and 0.60 (0.88) for OIR oxycodone (95% CI: 0.18–0.29; $p < 0.05$). The corresponding values for PID30 were 1.95 (1.47) and 1.60 (1.27) (95% CI: 0.30–0.45; $p < 0.05$). The percentage of episodes for which patients experienced meaningful pain relief in ≤ 15 minutes was 16% for FB tablets and 12% for OIR oxycodone (reported 95% CI for treatment difference: 1.1–2.0; $p < 0.05$). The corresponding values for ≤ 30 minutes were 45% and 36% (95% CI: 1.2–1.8; $p < 0.05$). The authors concluded that FB tablets provided more rapid analgesic effects than oxycodone and was well tolerated.

Overall, the results of active-controlled trials suggest that FPNS can achieve clinically meaningful pain reduction (PID ≥ 2.0) 5 minutes earlier than OIR morphine, about 10 minutes versus 15 minutes. FB tablet, OTFC lozenge, and OIR oxycodone do not achieve this magnitude of pain reduction until 30 minutes or later, when many episodes of CBTP are already spontaneously resolving. FPNS and OTFC lozenge produce greater magnitudes of pain reduction than OIR morphine; however, the differences in PID between treatments (≤ 0.5 points on an 11-point numerical rating scale) are of questionable clinical relevance. The number of *episodes* needed to treat (NeNT) for CMPR at 15 minutes was 16 for FPNS relative to OIR morphine and 10 for OTFC lozenge relative to OIR morphine (calculated NeNTs); and 25 for FB tablet relative to OIR oxycodone.

Placebo-controlled Trials

In placebo-controlled trials, the first onset of clinically meaningful difference in PID (≥ 2 points) occurred at 15 minutes with FSL tablet (1 RCT) and FPNS (1 RCT), and at 30 minutes with FB tablet (2 RCTs), FB film (1 RCT), and OTFC lozenge (1 RCT) (Table 11).

Table 11 PID at 5–30 Minutes in DB Placebo-controlled RCTs that Used 11-Point Numerical Rating Scales (ITT or FAS Analyses)

	Placebo		FSL Tab		FB Tab		FB Film		FPNS		OTFC Lozenge	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
5 min												
Slatkin 2007	0.2	DE			0.2	DE						
Rauck 2010	0.2	DE					0.21	DE				
Portenoy 2010	0.5	DE							0.6	DE		
10 min												
Rauck 2009	0.88	0.25	1.20*	0.25								
Slatkin 2007	0.50	0.09			0.90*	0.09						
Rauck 2010	0.62	0.12					0.75	0.12				
Portenoy 2010	0.7	DE							1.3*	DE		
15 min												
Rauck 2009	1.5	0.38	2.0*	0.38								
Portenoy 2006	0.48	0.10			0.93*	0.12						
Slatkin 2007	0.80	0.11			1.39*	0.13						
Rauck 2010	1.2	0.2					1.4	0.2				
Portenoy 2010	1.3	DE							2.0*	DE		
Farrar 1998	1.07	NR									1.65*	NR
30 min												
Rauck 2009	2.1	0.55	2.87*	0.30								
Portenoy 2006	1.40	0.20			2.30*	0.20						
Slatkin 2007	1.29	0.13			2.29*	0.18						
Rauck 2010	1.9	0.25					2.5*	0.20				
Portenoy 2010	1.6	DE							2.6*	DE		
Farrar 1998	1.60	NR									2.47*	NR

Sources: As noted in table plus Vissers (2010)[Error! Bookmark not defined.]
DE, Difficult to estimate from report; FAS, Full analysis set; ITT, Intent-to-treat; NR, Not reported; PID, Pain intensity difference (observation point – baseline)
* Indicates $p < 0.05$ for fentanyl TM IR formulation vs. comparator

In the placebo-controlled trial evaluating FSL spray, pain intensity was measured using a 100-mm VAS scale.[31] The onset of a clinically meaningful difference in PID was not assessed. The earliest statistically significant difference in PID and SPID between FSL spray and placebo occurred at 5 minutes.

Table 12 PID at 40–60 Minutes in DB Placebo-controlled RCTs that Used 11-Point Numerical Rating Scales (ITT or FAS Analyses)

	Placebo		FSL Tab		FB Tab		FB Film		FPNS		OTFC Lozenge	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
45 min												
Portenoy 2006	1.89	0.18			3.27*	0.23						
Slatkin 2007	1.43	0.13			2.86*	0.18						
Rauck 2010	2.25	0.31					3.0*	0.25				
Portenoy 2010	1.9	DE							3.0*	DE		
Farrar 1998	2.48	NR									3.11*	NR
60 min												
Rauck 2009	2.4	0.62	3.38*	0.50								
Portenoy 2006	2.26	0.21			3.96*	0.23						
Slatkin 2007	1.55	0.14			3.21*	0.20						
Rauck 2010	2.4	0.37					3.3*	0.25				
Portenoy 2010	2.0	DE							3.4*	DE		
Farrar 1998	2.79	NR									3.45*	NR

Sources: As noted in table plus Vissers (2010)[Error! Bookmark not defined.]
DE, Difficult to estimate from report; NR, Not reported. * Indicates $p < 0.05$ for fentanyl TM IR formulation vs. comparator.

Overall, the results of the placebo-controlled trials showed that FPNS and FSL tablet achieved clinically meaningful pain reduction (PID ≥ 2) at 15 minutes, whereas the other TIRF products did not achieve this outcome until 30 minutes or later, when CBTP episodes start to spontaneously resolve, as reflected in the PID results with placebo.

Systematic Reviews: Indirect Comparisons Among TIRF and OIR Morphine

Based on a fair-quality systematic review funded by Nycomed (manufacturer of INSTANYL IFNS), INSTANYL (the European INFS) seemed to achieve earlier and greater pain reduction, showing statistically significant differences in indirect comparisons at 15 and 30 minutes versus FB tablet; at 15, 30, and 45 minutes versus OTFC

lozenge; and at 15–60 minutes versus oral morphine.[32] In addition, because of a slow onset of effect (i.e., a statistically significant difference versus placebo in PID was reached at 40 minutes), oral morphine could not be considered an appropriate treatment for breakthrough cancer pain. FPNS was not included in the systematic review.

An update[33] to the systematic review described above added 3 RCTs of newer TIRF formulations: FPNS, FSL tablets, and FB film (1 RCT each).[34,35,36] A fourth RCT evaluated FPNS with OIR morphine.[37] The 95% CIs for the mean PID did not overlap between INFS and the other TIRF products and OIR morphine at 15 minutes. INFS achieved greater PID (95% CIs did not overlap) than the other TIRF products and OIR morphine, except 95% CIs overlapped with those of FPNS at 30 minutes. INFS was also better than FS tablet and FB film at 45 minutes but was similar to the other opioid products at this time point. INFS was better than FB film but not the other products at 60 minutes. Thus, INFS seemed to achieve earlier and greater pain reduction than the other six products at 15 minutes. Thereafter, FPNS provided pain reduction comparable to that of INFS. This systematic review was sponsored by INSTANYL's manufacturer, Takeda Pharmaceuticals International GmbH, which acquired its original manufacturer, Nycomed, in 2011.

In another systematic review / meta-analysis, mixed-treatment comparison including 4 placebo-controlled trials and 1 morphine-controlled trial, oral immediate-release morphine had a 56% probability of being superior to placebo in providing pain relief in the first 30 minutes after dosing, whereas the probabilities were 66% with FSL tablet, 73% with OTFC lozenge and 83% with FB tablet (all versus placebo).[31] When the TIRF agents were indirectly compared with oral morphine, the probabilities were 56% for FSL tablet, 58% for FB tablet and 62% for OTFC lozenge. A 50% probability represents equivalent efficacy; 67%, a 2:1 likelihood of superior efficacy; 75%, a 3:1 likelihood; and 99%, a 99:1 likelihood. The results suggested that oral morphine may adequately relieve breakthrough cancer pain but TIRF may provide clinical advantages for some patients.

Summary of phase-II clinical trial efficacy findings for FSL tablet[12]

- This multicenter, double-blind, four-period crossover study evaluated Orexo's FSL tablet.
- 38 patients received one dose of placebo, 100 mcg, 200 mcg, or 400 mcg fentanyl each day in random order to treat four episodes of breakthrough pain.
- The overall improvement in PID over the whole treatment period was significantly better for the 400-mcg dose compared to placebo (8.57 mm, $p<0.0001$). The treatment difference became statistically significant starting at 15 minutes post-dose (–23.65 vs. –16.10 mm). No significant difference was observed between the 100-mcg or 200-mcg doses compared to placebo.

Summary of phase-III clinical trial efficacy findings for FSL tablet[11]

- Of the 131 patients who entered the titration phase, 53 patients withdrew for the following reasons: AE (11.5%), protocol violation (10.7%), withdrawal of consent (7.6%), lack of efficacy (8.4%), and sponsor decision (2.3%)
- The primary endpoint of mean SPID30 was significantly greater for fentanyl-treated episodes than placebo (P=0.0004)
- PID was significantly greater for fentanyl-treated episodes than placebo at all points post-dose (10 to 60 minutes)
- Patient satisfaction was better for fentanyl than placebo (P=0.0006)
- More patients achieved ≥30% reduction in pain 30 minutes post-dose with fentanyl (86.9%) than placebo (64.9%) (NNT = 4.5)

Summary of clinical trial efficacy findings for FB film[13]

- The least-squares mean (LSM) ± the standard error of the mean (SEM) of the SPID30 (the primary efficacy endpoint, based on an 11-point numerical rating scale) was significantly greater for fentanyl-

treated episodes of breakthrough pain compared to placebo-treated episodes (47.9 ± 3.9 versus 38.1 ± 4.3; P = 0.004). Calculated effect size (Cohen's *d*) was 0.27, corresponding to a small effect.

- SPID values were consistently higher for fentanyl-treated episodes across all intervals, and differences from placebo were statistically significant at all intervals from 15 minutes to 60 minutes post-dose. The mean SPID60 (from a baseline of zero, estimated from Figure 2 of article) was 140 for FB film and 110 for placebo (p = 0.001). (Both treatments met the MCID cutoff value of 2 for adequate pain relief of CBTP.)
- Mean PID was significantly higher with FB film starting at 30 minutes (2.5 versus 1.8, estimated from Figure 3 of article) and lasted through 60 minutes (3.2 versus 2.4). (MCID of 2 for PID was met between 15 and 30 minutes with FB film and between 30 and 45 minutes with placebo.)
- PR values were significantly greater than placebo starting at 30 minutes post-dose until 60 minutes post-dose (data not reported; P < 0.01).
- The percentages of episodes with ≥33% decrease in pain were significantly greater (p ≤ 0.009) for fentanyl-treated episodes than placebo-treated episodes at 30 (47.3% vs. 38.2%), 45 (57.5% vs. 46.5%), and 60 minutes (64.3% vs. 48.2%). The corresponding values for ≥50% decrease in pain were 32.8% vs. 24.1, 41.1 vs. 30.5, and 46.3 vs. 34.0 at 30, 45, and 60 minutes, respectively. Number of episodes needed to treat for ≥33% and ≥50% pain reduction are shown in Table 13.
- Global satisfaction (rated on a 5-point scale from poor to excellent) was greater with FB film than placebo (mean score 2.0 vs. 1.5, P<0.001). A greater percentage of patients rated their global satisfaction as excellent, very good, or good on FB film (67.1%) than on placebo (47.1%).
- The results showed that FB film was consistently efficacious across these various outcome measures after 30 minutes but was not consistently efficacious at 15 minutes post-administration.

Table 13 Number of *Episodes* Needed to Treat (NeNT) to achieve ≥33% and >50% reduction in BTP

	Time post-administration (min)			
Reduction in Pain	**15**	**30**	**45**	**60**
≥33%	19.6	11.0*	9.1*	6.2*
≥50%	500.0	11.5*	9.4*	8.1*

NeNTs shown refer to FB film relative to placebo
* p < 0.05

Summary of clinical trial efficacy findings for FSL spray[31,38]

The major efficacy-safety trial for FSL spray used a 100-mm VAS for pain intensity measurements. The sum of PID30 (SPID30) was the primary efficacy measure. The mean (SD) SPID30 was 640.3 (458.8) for FSL spray and 399.6 (391.2) for placebo with a difference of 240.7 (362.9) (p < 0.0001; N = 92, evaluable population).

Table 14 Summary of clinical trial efficacy findings for FB tablet

Trial	Study Treatments	Design	Results	Number of *Episodes* Needed to Treat (NeNT) (95% CI)
Slatkin (2007)[15]	Patients assigned to one of 18 treatment sequences with 10 tablets; 7 FBT, 3 placebo.	MC PC DB RTC	The primary endpoint $SPID_{60}$ was significantly greater for FBT compared to placebo [9.7 ± 0.63 (SE) vs. 4.9 ± 0.50, P<0.001] *The MCID for SPID60 was met for both FB tablet and placebo	NeNT to achieve ≥33% and >50% improvements in PI scores from baseline: NeNT: Min 10: ≥33% 16.7, >50% 33.3; Min 15: ≥33% 6.7, >50% 10.0; Min 30: ≥33% 4.0, >50% 4.3
Portenoy (2006)[14]	Patients assigned to one of 18 treatment sequences with 10 tablets; 7 FBT, 3 placebo.	MC PC DB RTC	The primary endpoint $SPID_{30}$ was significantly greater for FBT than placebo (P<0.0001).	NeNT to achieve ≥33% and >50% improvements in PI scores from baseline: NeNT: Min 15: ≥33% 25.0, >50% 50.0; Min 30: ≥33% 5.3, >50% 12.5; Min 45: ≥33% 3.7, >50% 3.8; Min 60: ≥33% 3.7, >50% 3.4
Weinstein (2009)[16]	Once titrated to an effective dose, patients could treat up to 6 episodes of BTP per day with FB tablet.	Long-term OL MC extension study	Common AEs considered to be treatment related were nausea (10%), constipation (8%), dizziness (6%), and somnolence (6%). No clinically meaningful trends were observed in lab values or physical or neurologic exam; any changes observed were considered consistent with the underlying condition.	N/A

Table 15 Summary of clinical trial efficacy findings for FPNS

Trial	Study Treatments	Design	Results	NNT (95% CI) or NeNT
Portenoy (2010)[17]	Patients randomized to a treatment sequence with 10 nasal spray bottles; 7 FPNS and 3 placebo.	MC PC DB CO RTC	The primary endpoint of SPID30 was significantly greater for FPNS-treated patients than placebo (P < 0.0001).	Percentage of patients with clinically meaningful pain relief (≥2-point reduction in summed pain intensity difference) Treatment: Time post Dose (min) / FPNS / Placebo / P / NNT 10: 38.4 / 23.3 / ≤0.01 / 6.6 15: 64.4 / 45.2 / ≤0.01 / 5.2 30: 82.2 / 60.3 / ≤0.0001 / 4.6 45: 89.0 / 69.9 / ≤0.001 / 5.2 60: 95.9 / 74. / ≤0.0001 / 4.6
Taylor (2010)[18]	Patients randomized to a treatment	MC PC DB	Significantly more BTP episodes treated with FPNS than placebo had a ≥1-point	≥2-point (clinically meaningful) reduction in PI and SPID PI (% episodes)

	sequence with 10 nasal spray bottles; 7 FPNS and 3 placebo.	RTC	reduction in pain intensity across all time points (5 – 60 minutes) and a ≥2-point reduction at 10 – 60 minutes. SPID was significantly better for FPNS-treated episodes at 10 – 60 minutes.	

Min	FPNS	Placebo	NeNT
5	13.1	11.5	62.5
10	32.9	24.5	11.9
15	50.8	32.0	5.3
30	65.8	40.0	3.9
45	70.8	45.5	4.0
60	76.3	48.5	3.6

	SPID (% episodes)		
Min	FPNS	FPNS	FPNS
5	--	--	--
10	41.0	30.0	9.1
15	62.7	45.0	5.6
30	76.3	56.0	4.9
45	85.4	61.0	4.1
60	89.1	65.5	4.2

Table 16 Summary of clinical trial efficacy findings for OTFC lozenge

Trial	Study Treatments	Design	Results	Minimal Clinically Important Difference (MICD)
Farrar (1998)[26]	OTFC lozenge titrated to an effective dose of 200-1600 µg during an open-label titration. Patients were randomized to a treatment sequence with 10 tablets; 7 OTFC lozenge and 3 placebo. Throughout the double-blind study, 804 BTP episodes were treated; 247 with placebo and 557 with OTFC lozenge.	MC PC DB CO RTC	PID and PR were significantly better for OTFC lozenge than placebo at all time points (P<0.0001) Mean global performance evaluation was 1.98 for OTFC lozenge and 1.19 for placebo (P<0.0001) More patients (34%) required rescue medication for BTP episodes treated with placebo than episodes treated with OTFC lozenge (15%) [relative risk = 2.27; P<0.0001)	Mean PID and PR

	PID			
	Minutes			
Treatment	15	30	45	60
OTFC lozenge	1.62	2.41*	2.88*	3.19*
Placebo	1.02	1.51	1.91	2.13*

	PR			
	Minutes			
Treatment	15	30	45	60
OTFC lozenge	1.42	1.80	2.00*	2.14*
Placebo	0.93	1.11	1.30	1.33

*Values met MCID

Trial	Study Treatments	Design	Results	
Rauck (2012)[22]	Patients randomized to a treatment sequence with 10 SL spray doses; 7 FSL spray doses and 3 PBO doses	MC DB PC CO RCT	Mean SPID30 score was 640.3 with FSL spray and 399.6 with PBO (P<0.0001). Signifcant differences in PID and SPID scores for BTP episodes were seen at all intervals from 5 to 60 min.	Mean SPID and PR

	SPID			
	Minutes			
Treatment	5	15	30	60
FSL Spray	40.3	220.6	640.3	1649.0
PBO	32.0	150.3	399.6	965.7

	PR			
	Minutes			
Treatment	5	15	30	60
FSL Spray	8.6	32.9	78.3	176.4
PBO	7.6	27.1	61.0	131.2

Cochrane Review
A Cochrane Review of four trials reviewing OTFC lozenge concluded that OTFC lozenge showed superiority to placebo, and that this product must be titrated to an effective dose due to the lack of relationship between the effective dose and dose of ATC opioid therapy.[39]

Adverse Events (Safety Data)

FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray are classified Schedule-II (CII).

Deaths and Other Serious Adverse Events

Respiratory depression is the main risk associated with opioid therapy, including FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray.

Common Adverse Events

The table below describes the most common adverse effects observed during the titration phase in clinical trials of FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray.

Table 17 Common Adverse Reactions Observed During Dose Titration

Adverse Effect	FSL TABLET (N = 270) %	FB FILM (N = 306) %	FB TABLET (N = 304) %	FPNS (N =516) %	OTFC LOZENGE (N=254) %	FSL SPRAY (N=359) %
Nausea	5.6	14	17	7	23	13.1
Vomiting	--*	8	5	6	12	10.3
Dizziness	2.2	7	19	6	17	7.2
Headache	1.9	6	9	--	6	--
Somnolence	4.4	--	7	--	17	9.5
Fatigue	--	--	6	--	--	--

*Events were marked as (--) when no data was available for that treatment.

The table below illustrates the incidence of adverse effects observed during the maintenance phase in clinical trials of FSL tablet, FB film, FB tablet, FPNS, FSL spray, OTFC lozenge and FSL spray.

Table 18 Common Adverse Reactions Observed During Maintenance

Adverse Effect by Body System	FSL TABLET (N = 168) %	FB FILM (N = 213) %	FB TABLET (N = 200) %	FPNS (N = 346) %	OTFC LOZENGE (N=152) %	FSL SPRAY (N=269) %
Gastrointestinal						
Nausea	6.0	26	29	7	45	10.4
Vomiting	--*	21	20	10	31	16.0
Constipation	4.8	11	12	6	20	10.4
Diarrhea	--	19	8	--	--	--
Dry Mouth	1.8	7	--	--	4	--
Abdominal Pain	--	5	9	--	--	--
Stomatitis	1.8	--	--	--	--	--

Adverse Effect by Body System	FSL TABLET (N = 168) %	FB FILM (N = 213) %	FB TABLET (N = 200) %	FPNS (N = 346) %	OTFC LOZENGE (N=152) %	FSL SPRAY (N=269) %
Nervous System						
Headache	3.0	9	10	--	20	--
Somnolence	--	7	9	--	15	--
Dizziness	--	11	13	--	16	--
Dysgeusia	1.2	--	--	--	--	--
General/Administration Site						
Fatigue	1.8	12	16	--	--	--
Asthenia	--	13	11	--	38	9.7
Respiratory						
Dyspnea	0.6	12	--	--	22	10.4
Cough	--	7	--	--	--	--
Metabolism and Nutrition						
Dehydration	--	13	11	--	--	--
Anorexia	--	8	8	--	--	--
Investigations						
Weight Decrease		7	7	--	--	--

*Events were marked as (--) when no data was available for that treatment.

Other commonly reported adverse events with FB film include confusion (8%), depression (8%), anxiety (5%), insomnia (6%), hypotension (5%), weight loss (7%), dehydration (13%), decreased appetite (8%), and anorexia (8%).**Error! Bookmark not defined.**

Adverse events reported with FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray were typical of those commonly seen with opioid therapy in patients with cancer.

Tolerability

FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray were generally well tolerated in clinical trials and observed adverse events were typical of opioid therapy.

Contraindications

FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray are contraindicated in opioid non-tolerant patients, as well as for the treatment of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room.

REMS Restricted Access Programs

A shared REMS system strategy, called the TIRF REMS Access Program began on March 12th, 2012. All TIRF products will be covered under this one restricted access program. Further information is available at www.fda.gov and the TIRF REMS Web site (www.TIRFREMSaccess.com). Further information on VA requirements for TIRF REMS is located on the PBM INTRAnet site under Special Handling Drugs.

Sentinel Events

None.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

Table 19 Look-Alike / Sound-Alike Drug Names

Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Fentanyl	Alfentanil Sufentanil	Sufentanil	Sufentanil	Potential for mix-up among all TM fentanyl products
ABSTRAL sublingual	None	None	None	ACTIGALL ACTONEL
ONSOLIS buccal film	None	None	None	OMNARIS
FENTORA buccal tab	None	None	None	FEMARA
LAZANDA nasal spray	None	None	None	LATUDA
ACTIQ lozenge	None	None	None	ACTOS
SUBSYS Sublingual spray	None	None	None	SUBOXONE SUBUTEX SUBLIMAZE ZUBSOLV

Look-alike / Sound-alike names as of July 2016

Conclusions

Transmucosal immediate-release fentanyl (TIRF) products have been shown in short-term, controlled clinical trials to be relatively safe and efficacious in the treatment of breakthrough pain in patients who are currently on opioid therapy for persistent cancer-related pain. Potential advantages of FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray over other oral opioids include avoidance of first-pass metabolism, moderately faster onset of action, and an alternative method of administration in patients with dysphagia, nausea, or vomiting. Additional rescue medications may still be necessary if breakthrough pain is not relieved by the fentanyl product, as the number of doses allowed per episode and per day are limited, with FB film and FPNS allowing only one dose per episode (as compared with 2 doses for the other formulations).[1,2]

There have been no direct efficacy and safety comparisons among the different TIRF formulations available in the U.S. In a direct comparison with oral immediate-release (OIR) morphine, FPNS achieved a greater magnitude of pain reduction that was statistically significant but of questionable clinical importance, and reached a clinically meaningful pain reduction (PID $\geq$ 2) less than 5 minutes earlier than OIR morphine. In indirect comparisons, FPNS and OIR morphine seemed to achieve PID $\geq$ 2 faster than FB tablet, OTFC lozenge, and OIR oxycodone (by at least 20 minutes for each).

FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray doses must be individually titrated and are not interchangeable. If a TIRF product is considered for addition to the VA National Formulary, it may be wise to add only one TIRF product to reduce the potential for inappropriate conversions between different TIRF products, and to restrict its use to patients who are opioid-tolerant, have severe, recurrent, *unpredictable* cancer-related breakthrough pain (CBTP), and are unable to take or tolerate OIR morphine. Providers should be educated that, in contrast to immediate-release rescue opioids, the dose of TIRF products must be titrated rather than calculated as a percentage of the around-the-clock opioid dose.

Because FSL tablet, FB film, FB tablet, FPNS, OTFC lozenge and FSL spray are not dose equivalent with other opioids, specific dose titration guidelines must be followed when initiating these drugs to reduce the risk of respiratory depression, and close follow-up may be necessary during initiation.[1,2] This titration requirement may make the use of these products difficult for some outpatients. The possibility of patients having to use multiple units during the titration phase may be complicated and time consuming.[40]

The value of these products in the inpatient setting is limited due to the involved titration process and lack of proven benefit over IV morphine, which is easily dosed and administered but requires intravenous access.

As of March 12, 2012, providers, pharmacies, and patients must be enrolled in the shared Transmucosal Immediate-release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program, to prescribe, dispense, and receive TIRF products. This REMS program may help to mitigate misuse, abuse, addiction, and diversion of TIRF products, but the fast-on, fast-off properties of these agents still make them highly desirable drugs of abuse. The potential risks and benefits of TIRF products need to be carefully weighed on an individualized basis. TIRF therapy will require diligent opioid risk assessment and monitoring as part of a comprehensive, multidisciplinary approach to pain management in patients with CBTP.

Updated August 2016 (added FSL spray). Previously updated November 2013.
Originally prepared in April 2012 by Kaitlyn McDowell, PharmD and Francine Goodman, PharmD, BCPS.
Contact person: Francine Goodman, Clinical Pharmacy Specialist, Pharmacy Benefits Management Services

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to August 2011) using the search terms <fentanyl>, <ABSTRAL>, <ONSOLIS>, <FENTORA>, <LAZANDA>, <administration, buccal>, <administration, sublingual>, and <nasal sprays>. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Summary of Trials Evaluating Transmucosal Immediate-release Fentanyl in CBTP

<table>
<tr><td>Citation</td><td>Rauck RL, Tark M, Reyes E et al. Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. Curr Med Res Opin 2009;25(12):2877-85</td></tr>
<tr><td rowspan="3">Study Design/ Methodology</td><td>MC, PC, R, Phase III trial</td></tr>
<tr><td>Efficacy Analysis – Primary Criteria for Evaluation</td></tr>
<tr><td>SPID30</td></tr>
<tr><td rowspan="5">Population</td><td>Inclusion Criteria</td></tr>
<tr><td>• Patients aged 17 and older with stable cancer-related pain treated with ATC opiods.
• Experiencing 1 to 4 episodes of BTP per day</td></tr>
<tr><td>Exclusion Criteria</td></tr>
<tr><td>• Uncontrolled or rapidly escalating pain.
• MAOI treatment within 14 days of study entry.</td></tr>
<tr><td>• PP Efficacy N = 61 of 131 patients titrated; 393 FSL tablet-treated episodes, 168 placebo-treated episodes.
• Safety N = 72
<table>
<tr><th></th><th>N</th><th>Age (mean)</th><th>Male (%)</th><th colspan="4">Race</th></tr>
<tr><td></td><td></td><td></td><td></td><td>White</td><td>Black</td><td>Asian</td><td>Other</td></tr>
<tr><td>Efficacy</td><td>66</td><td>53.3</td><td>47.0</td><td>84.8</td><td>1.5</td><td>3.0</td><td>10.6</td></tr>
<tr><td>Safety</td><td>72</td><td>53.6</td><td>45.8</td><td>84.7</td><td>2.8</td><td>2.8</td><td>9.7</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>• Patients were titrated to an effective dose of 100 mcg to 800 mcg during a 2-week open-label titration phase.
• If successfully titrated, patients were randomized to a sequence of 10 doses; seven FSL tablet and 3 placebo.
• Rescue medication was permitted if a BTP episode occurred within 2 hours of study drug treatment.
• If patients completed the 10-dose efficacy phase, they were eligible to enter an open-label long-term safety phase of up to 12 months.
• PI and PR were measured at 0, 10, 15, 30, and 60 min post-dose.</td></tr>
</table>

Results	**Efficacy**
	• The primary endpoint of mean SPID30 was significantly greater for FSL tablet-treated episodes than placebo (49.5 vs. 36.6, P=0.0004) • Significant improvements in PID were seen as early as 10 min and up to 60 min post dose when comparing FSL tablet vs. placebo (P = 0.0055 and P≤0.0055, respectively). • FSL tablet provided significantly greater pain relief than placebo from 10 to 60 min post-dose (P≤0.049). • Mean global assessment scores were greater for FSL tablet than placebo (3.1 vs. 3.6, P = 0.0006) • Rescue medication was required in 11.2% of FLS tablet-treated episodes, vs. 27.4% placebo-treated episodes. • More patients achieved ≥30% reduction in pain 30 minutes post-dose with FSL LOZENGE (86.9%) than placebo (64.9%) (NeNT = 4.5)
	Safety
	• A total of 38,015 episodes of BTP were treated with FSL tablet over a median of 161.5 days during the long-term safety phase. • The most common AEs were nausea (12.2%), vomiting (5.3%), and somnolence (4.6%). • Thirty patients withdrew due to AEs; 17 of these AEs were considered to be possibly or probably related to study drug and included dyspnea, nausea, and vomiting.
Author's Conclusion	This phase III clinical trial demonstrated that FSL tablet is superior to placebo in treating BTP associated with cancer, and that the drug is generally safe and well-tolerated.
Critique	Jadad Score: 4

Citation	Lennernas B, Frank-Lissbrant I, Lennernas H, Kalkner KM, Derrick R, Howell J. Sublingual administration of fentanyl to cancer patients is an effective treatment for breakthrough pain: results from a randomized phase II study. *Palliat Med* 2010;24(3):286-93
Study Design/ Methodology	MC, DB, CO, RCT
	Efficacy Analysis – Primary Criteria for Evaluation
	PID
Population	Inclusion Criteria
	• Patients aged 18 – 90 with cancer. • Using ATC opiods for chronic pain. • Experiencing at least 4 episodes of BTP over 14 days.
	Exclusion Criteria
	• Signs of organ disease or progressive cancer that could interfere with the study. • Use of any other investigational drugs within past 8 weeks, except anti-cancer drugs.
	• Mean age – 63 (female); 65 (male) • Sex (n) – 10 female; 13 male • Race – white (100%) • Per-protocol set N = 23 • ITT N = 27 • Safety N = 38
Intervention	• Patients received one dose each of placebo, 100 mcg, 200 mcg, and 400 mcg FSL tablet in random order to treat four episodes of breakthrough pain. • A washout period of at least 1 day was used between treatment periods.

	• PI was recorded at 0, 5, 10, 15, 20, and 30 minutes post-dose.
Results	**Efficacy**
	• PID was significantly better for the 400-mcg dose compared to placebo starting at 15 minutes post-dose through 25 minutes; no significant difference was observed between the 100-mcg or 200-mcg doses compared to placebo. • Global assessment rating of excellent was given by 9 patients for the 400 mcg dose, 3 for the 200 mcg dose, 5 for 100 mcg, and 3 for placebo. • Twenty-two patients (95%) who completed all four treatments identified at least one dose of FSL tablet that produced a decrease in PID of >33%.
	Safety
	• Study drugs were well tolerated. The most common AEs were pain (n = 4) and vomiting (n = 2).
Author's Conclusion	PID was significantly improved compared to placebo starting at 15 min post-dose for the 400 mcg dose. 100 mcg and 200 mcg doses also showed reductions in PID.
Critique	Jadad Score: 5

Citation	Rauck R, North J, Gever LN, Tagarro I, Finn AL. Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. *Ann Oncol* 2010;21(6):1308-14
Study Design/ Methodology	MC, DB, PC, CO, RCT
	Efficacy Analysis – Primary Criteria for Evaluation
	SPID30
Population	Inclusion Criteria
	• Patients aged 18 years and older with cancer-related pain being treated with opioids. • Experiencing one to four BTP episodes per day, with at least partial relief of episodes from opioids.
	Exclusion Criteria
	• Pregnant or lactating. • Experiencing >4 BTP episodes per day. • Rapidly escalating pain.
	• Mean age – 56.8 • Sex – 45% male; 55% female • Race – 90.0% white; 7.5% black; 2.5% other • ITT N = 80; 394 FB film-treated episodes and 197 placebo-treated episodes • Safety N = 151
Intervention	• Patients who identified an effective dose during the open-label titration phase that provided satisfactory analgesia for two BTP episodes entered the study. • During the double-blind study, patients were randomized to a sequence of nine doses; six FB film and three placebo. No patients received two placebos in a row. • If adequate analgesia was not achieved within 30 minutes, patients were permitted to use a rescue medication. • PI and PR were assessed at 5, 10, 15, 30, 45, and 60 min post dose.

<table>
<tr><td>Results</td><td>Efficacy
The least-squares mean (LSM) ± the standard error of the mean (SEM) of the SPID30 was significantly greater for FB film-treated episodes compared to placebo-treated episodes (47.9 ± 3.9 versus 38.1 ± 4.3; P = 0.004). Calculated effect size (Cohen's d) was 0.27, corresponding to a small effect.
SPID values were consistently higher for FB film-treated episodes across all intervals, and differences from placebo were significant at all intervals from 15 minutes to 60 minutes post-dose.
PR was significantly better for FB film starting at 30 min post-dose (P<0.01) through 60 min post-dose (P<0.01).
Global satisfaction was greater with FB film than placebo (mean score 2.0 vs. 1.5, P<0.001)
The percentage of episodes with both ≥33% and >50% decrease in pain was significantly greater for FB film-treated episodes than placebo-treated episodes at 30, 45, and 60 minutes.
Number of Episodes Needed to Treat (NeNT) to achieve ≥33% and >50% reduction in BTP<table><tr><th rowspan="2">Reduction in Pain</th><th colspan="4">Time post-administration (min)</th></tr><tr><th>15</th><th>30</th><th>45</th><th>60</th></tr><tr><td>≥33%</td><td>19.6</td><td>11.0*</td><td>9.1*</td><td>6.2*</td></tr><tr><td>>50%</td><td>500.0</td><td>11.5*</td><td>9.4*</td><td>8.1*</td></tr></table>NeNTs shown refer to FB film relative to placebo
* p < 0.05
Safety
Twenty-three patients (15.2%) experienced 29 serious AEs, none of which were determined to be related to the study drug.
Twenty-one patients (13.9%) discontinued the study due to treatment-emergent AEs, the most common of which was nausea and vomiting (3.3% patients)</td></tr>
<tr><td>Author's Conclusion</td><td>FB film was superior to placebo and was well-tolerated when treating cancer-related BTP.</td></tr>
<tr><td>Critique</td><td>Jadad Score: 4</td></tr>
</table>

<table>
<tr><td>Citation</td><td>Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. Clin J Pain 2006;22(9):805-11</td></tr>
<tr><td rowspan="3">Study Design/ Methodology</td><td>MC, DB, PC, RCT</td></tr>
<tr><td>Efficacy Analysis – Primary Criteria for Evaluation</td></tr>
<tr><td>SPID30</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td></tr>
<tr><td>• ≥18 years old with chronic cancer pain and 1-4 episodes BTP per day
• Taking ATC opioids for at least 1 week
• BTP adequately controlled on a stable dose of short-acting opioid
• Life expectancy ≥3 months</td></tr>
<tr><td>Exclusion Criteria</td></tr>
<tr><td></td><td>• Treatment with intrathecal opioids
• Mucositis or stomasitis grade 2 or higher
• Sleep apnea, active brain metastases, increased intracranial pressure, COPD, impaired hepatic or renal function, pregnancy or lactating.</td></tr>
</table>

<table>
<tr><td></td><td>
• Mean Age – 57.5
• Sex – 55% male; 45% female
• Race – 88% white; 1% black; 10% other
• ITT N = 73; Efficacy N = 68; 493 FB tablet-treated episodes, 208 placebo
• Safety N = 123

Mean mg/d morphine equivalents of ATC medication – 213.5 ± 461.9
ATC opioids (%) – fentanyl (oral) (2), fentanyl (transdermal) (28), metadone (8), morphine (34), oxycodone (36), vicodin (7), other (10).
Supplemental opioid usage (%) – hydrocodone (7), hydromorphone (11), morphine (17), oxycodone (13), oxycodone/apap (24), vicodin (21), other (8).
</td></tr>
<tr><td>Intervention</td><td>
• FB tablet titrated to an effective dose of 100 – 800 µg during an open-label titration phase.
• Patients randomized to 1 of 18 treatment sequences with 10 tablets; 7 FB tablet and 3 placebo, all to be taken within 21 days at a max of 4 tabs/day.
• Throughout the titration phase and study phase, ATC opioid therapy was continued and patients were allowed to supplement with their former BTP treatment if relief was not achieved within 30 minutes of using FB tablet, or if treatment of >4 BTP episodes/day was required.
</td></tr>
<tr><td>Results</td><td>Efficacy</td></tr>
<tr><td></td><td>
• The primary endpoint $SPID_{30}$ was significantly greater for FB tablet than placebo (3.0 ± 0.12 vs. 1.8 ± 0.18, P<0.0001).
• Improvements in PI from baseline were significantly better for FB tablet vs. placebo at all time points (P<0.003 at 15 minutes; P<0.0001 for 30, 45, and 60 minutes).
• Percentage of patients achieving ≥33% pain reduction from baseline was significantly greater for FB tablet than placebo at all time points (P<0.05 at 15 min, P<0.0001 at 30, 45, and 60 min). Percentage achieving >50% reduction was significantly greater for FB tablet at 30 min (P<0.05), 45, and 60 min (P<0.001). NeNT shown in the table below.
<table>
<tr><td></td><td colspan="2">NeNT</td></tr>
<tr><td>Min</td><td>≥33%</td><td>>50%</td></tr>
<tr><td>15</td><td>25.0</td><td>50.0</td></tr>
<tr><td>30</td><td>5.3</td><td>12.5</td></tr>
<tr><td>45</td><td>3.7</td><td>3.8</td></tr>
<tr><td>60</td><td>3.7</td><td>3.4</td></tr>
</table>
• Supplementation with former BTP medication was used in 23% of FB tablet -treated episodes vs. 50% of placebo-treated episodes.
</td></tr>
<tr><td></td><td>Safety</td></tr>
<tr><td></td><td>
• Adverse effects occurring in ≥5% patients included nausea (22%), dizziness (22%), headache (15%), fatigue (12%), vomiting (11%), somnolence (10%), constipation (8%), asthenia (7%).
• Two (2%) patients had application-site reaction that resulted in their withdrawal from the study.
• Seven patients died during the study due to disease progression.
</td></tr>
<tr><td>Author's Conclusion</td><td>FB tablet provides fast and effective analgesia when treating BTP.</td></tr>
<tr><td>Critique</td><td>Jadad Score: 3</td></tr>
</table>

Citation	Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol* 2007;5(7):327-34

Study Design/ Methodology	MC, DB, PC, RCT
	Efficacy Analysis – Primary Criteria for Evaluation
	SPID60
Population	Inclusion Criteria
	• Age 18-80 • Cancer diagnosis causing cancer-related pain • Life expectancy >2 months • Using a fixed dose of ATC opioid • Average pain intensity of <7 on a scale of 0-11 • One to four BTP episodes per day • At least partial relief from opioids for BTP
	Exclusion Criteria
	• Uncontrolled pain that was not BTP • Sleep apnea, active brain metastases, increased intracranial pressure • History of alcohol or substance abuse in past 5 years • Cardiopulmonary disease that may affect study drug's safety • Previous participation in a FB tablet study
	• Mean Age – 53.9 • Sex – 38% male; 62% female • Race – 79% white; 8% black; 13% other • Mean BMI – 28.0 • Efficacy N = 78; 493 FB tablet-treated episodes, 223 placebo • Safety N = 125 Mean mg/d morphine equivalents of ATC medication – 279.2 ± 362.28 ATC opioid usage (%) – oxycodone/oxycodone-apap (36), fentanyl (32), morphine (20), methadone (12), hydromorphone (6), hydrocodone/apap (5), fentanyl citrate (<1), codeine/asa/carisoprodol (<1) BTP opioid usage - oxycodone/oxycodone-apap (43), hydrocodone/hydrocodone-apap (22), fentanyl citrate (12), hydromorphone (12), morphine (9), methadone (<1), codeine/apap (<1)
Intervention	FB tablet titrated to an effective dose of 100 – 800 µg during an open-label titration phase. Patients randomized to 1 of 18 treatment sequences with 10 tablets; 7 FB tablet and 3 placebo. Throughout the titration phase and study phase, ATC opioid therapy was continued and patients were allowed to supplement with their former BTP treatment if relief was not achieved within 30 minutes of using FB tablet.

<table>
<tr><td rowspan="3">Results</td><td>Efficacy</td></tr>
<tr><td>

The primary endpoint SPID60 was significantly greater for FB tablet compared to placebo [9.7 ± 0.63 (SE) vs. 4.9 ± 0.50, P<0.001]
PID were significantly greater for FB tablet from 10 minutes up to 120 minutes (P<0.0001 for all points)
Patient assessment of pain relief was better for FB tablet than placebo at 60, 90, and 120 minutes (P<0.0001)
Supplemental medication was used for 11% of BTP episodes treated with FB tablet vs. 30% episodes treated with placebo (NeNT=5.3).
Improvement in PI scores from baseline of ≥33% and >50% was significantly greater at all time points for FB tablet than placebo; NeNT displayed in table below

<table>
<tr><td></td><td colspan="2">NeNT</td></tr>
<tr><td>Min</td><td>≥33%</td><td>>50%</td></tr>
<tr><td>10</td><td>16.7</td><td>33.3</td></tr>
<tr><td>15</td><td>6.7</td><td>10.0</td></tr>
<tr><td>30</td><td>4.0</td><td>4.3</td></tr>
</table>
</td></tr>
<tr><td>Safety</td></tr>
<tr><td>

Adverse effects occurring in ≥5% patients included nausea (13%), dizziness (11%), fatigue (8%), and headache, vomiting, and constipation (6% each).
Application site reactions occurred in 10% of patients, most during the titration phase and were mild and transitory. One patient d/c the study due to application site irritation.
Nine patients died during the study, all from progression of underlying cancer.
No clinically significant laboratory changes or vital signs were observed.

</td></tr>
<tr><td>Author's Conclusion</td><td>FBT is effective in treating BTP as soon as 10 minutes and up to 2 hours post-dose.</td></tr>
<tr><td>Critique</td><td>Jadad Score: 4</td></tr>
</table>

<table>
<tr><td>Citation</td><td>Weinstein SM, Messina J, Xie F. Fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic cancer pain: A long-term, open-label safety study. Cancer 2009;115(11):2571-9.</td></tr>
<tr><td rowspan="3">Study Design/ Methodology</td><td>Long-term, OL, MC extension study.</td></tr>
<tr><td>Efficacy Analysis – Primary Criteria for Evaluation</td></tr>
<tr><td>AEs, physical and neurological exams, laboratory tests.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td></tr>
<tr><td>

Patients from 2 previous FB tablet studies who were adequately controlled on FB tablet were invited to continue in this long-term study.
New patients were also enrolled.
Patients 18 years and older with a diagnosis of cancer and a life expectancy of ≥2 months.
Opioids tolerant at a fixed dose of ATC opioids.

</td></tr>
<tr><td>Exclusion Criteria</td></tr>
<tr><td>

Sleep apnea, active brain metastases with increased intracranial pressure, COPD, abnormal renal or hepatic function test results.
Recent history of substance abuse or neurologic or psychiatric impairment.
Pregnant or lactating.

</td></tr>
</table>

	• Mean age – 55.3 • Sex – 47% male; 53% female • Race – 84% white; 7% black; 9% other • Mean BMI – 26.7 ATC opioid usage – 36% oxycodone; 33% fentanyl; 27% morphine; 9% methadone. Supplemental opioid usage – 35% oxycodone; 28% hydrocodone/apap; 13% morphine; 13% hydromorphone; 7% fentanyl citrate. • Overall safety N = 232 • Titration safety N = 112 • Maintenance safety N = 197
Intervention	• New study patients not rolling over from previous trials were titrated to an effective dose of FB tablet. • FB tablet could be used to treat a maximum of 6 BTP episodes per day, using a maximum of 8 tablets. If adequate analgesia was not achieved within 30 minutes of a dose, a second dose could be taken for that episode. • Vital signs and AEs were checked monthly; laboratory tests and oral mucosa exams were done every 3 months; neurologic and physical exams were performed every 3 months for the first 12 months, then ever 6 months thereafter. • Global Medication Performance assessment was rated by patients daily. • A patient survey was added during the study and completed by 25% of patients comparing FB tablet to their previous BTP medication. • Investigators were permitted to adjust patient doses as needed throughout the study.
Results	**Efficacy**
	• After one month, patients rated FB tablet higher than their previous BTP medication in overall preference (88% vs. 12%), time to onset of relief (95% vs. 5%), ease of administration (66% vs. 34%), and convenience of use (68% vs. 32%). • On a 5-point scale of 0 (poor) to 4 (excellent), the mean Global Medication Performance score was 2.4 at the start of the maintenance phase and 2.3 at the endpoint.
	Safety
	• The most common occurring AEs (≥15%) were nausea (32%), vomiting (24%), dizziness (11%), fatigue (18%), constipation (15%), anemia (15%), and peripheral edema (15%). • Common AEs considered to be treatment related were nausea (10%), constipation (8%), dizziness (6%), and somnolence (6%). • Application site AEs occurred in 6% of patients overall and included pain, irritation, paresthesia, and ulcer. Four patients withdrew from the study due to application site AEs. • A total of 77 patients withdrew due to AEs, 53 of which due to AEs related to the patients' underlying condition. • Three patients had a history of mucositis before entering the study. Five patients developed mucositits during the study, none of which were considered to be related to study drug. • No clinically meaningful trends were observed in lab values or physical or neurologic exam; any changes observed were considered consistent with the underlying condition.
Author's Conclusion	FB tablet was well-tolerated long-term and did not produce any AEs not expected when treating cancer patients with opioid medications.
Critique	Jadad Score: 1

<table>
<tr><td>Citation</td><td>Portenoy RK, Burton AW, Gabrail N, Taylor D. A multicenter, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain. Pain 2010;151(3):617-24.</td></tr>
<tr><td rowspan="3">Study Design/ Methodology</td><td>MC, DB, PC, CO, RCT</td></tr>
<tr><td>Efficacy Analysis – Primary Criteria for Evaluation</td></tr>
<tr><td>SPID30</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td></tr>
<tr><td>• Confirmed cancer diagnosis
• Opioid-tolerant
• Experiencing 1 – 4 episodes of BTP per day</td></tr>
<tr><td>Exclusion Criteria</td></tr>
<tr><td>• Rapidly escalating pain or medically unstable
• Pain unrelated to cancer
• History of drug or alcohol abuse
• Treatment with MAOI</td></tr>
<tr><td>Intervention</td><td>• Patients were titrated to an effective dose of 100 - 800µg during an open-label titration phase.
• Patients randomized to a treatment sequence with 10 nasal spray bottles; 7 FPNS and 3 placebo.</td></tr>
<tr><td rowspan="3">Results</td><td>• ITT Efficacy population N = 83; 459 FPNS BTP episodes; 200 placebo BTP episodes
• Safety population N = 113
• Mean age – 53.8
• Sex – 53.1% male; 46.9% female
• Race – 68.1% white; 11.5% black; 20.4% other

Opioid use(%)* - Propoxyphene/APAP (0.9); methadone (20.4); hydromorphone (6.2); morphine (39.9); oxycodone/APAP (8.0); oxycodone (23.0); hydrocodone/APAP (6.2); hydrocodone (4.4); tramadol (0.9); fentanyl (23.9)
*Some patients used >1 opioid medication.</td></tr>
<tr><td>Efficacy
• The primary endpoint of SPID30 was significantly greater for FPNS-treated patients than placebo (6.57 ± 4.99 vs. 4.45 ± 5.51, respectively; P < 0.0001).
• PI scores were significantly lower in FPNS-treated episodes than placebo at all time points.
• The percentage of patients with clinically meaningful pain relief (≥2-point reduction in summed pain intensity difference) was significantly greater for FPNS than placebo at all time points.

Percentage of patients with clinically meaningful pain relief
<table>
<tr><td></td><td colspan="3">Treatment</td><td></td></tr>
<tr><td>Time Post-Dose (min)</td><td>FPNS</td><td>Placebo</td><td>P</td><td>NeNT</td></tr>
<tr><td>10</td><td>38.4</td><td>23.3</td><td>≤0.01</td><td>6.6</td></tr>
<tr><td>15</td><td>64.4</td><td>45.2</td><td>≤0.01</td><td>5.2</td></tr>
<tr><td>30</td><td>82.2</td><td>60.3</td><td>≤0.0001</td><td>4.6</td></tr>
<tr><td>45</td><td>89.0</td><td>69.9</td><td>≤0.001</td><td>5.2</td></tr>
<tr><td>60</td><td>95.9</td><td>74.0</td><td>≤0.0001</td><td>4.6</td></tr>
</table>
</td></tr>
<tr><td>Safety
AEs were more common with FPNS treatments than placebo and included vomiting (10.6%), nausea (8.8), and dizziness (8.0). One event of non-cardiac chest pain was considered to be related to FPNS; all others were deemed not to be drug related. Eight patients died during the study due to disease progression.</td></tr>
</table>

Author's Conclusion	The authors concluded that FPNS was efficacious and well tolerated in treating BTP in patients with cancer pain. Pain relief was seen as early as 5 minutes and lasted up to 60 minutes.
Critique	Jadad Score: 5

Citation	Taylor D, Galan V, Weinstein SM, Reyes E, Pupo-Araya AR, Rauck R. Fentanyl pectin nasal spray in breakthrough cancer pain. *J Support Oncol* 2010;8(4):184-90.
Study Design/ Methodology	MC, DB, PC, CO, RCT – additional results from Portenoy (2011)**Error! Bookmark not defined.** Reported on consistency of efficacy (per-episode analyses and rescue medication use), nasal tolerability, and patient acceptability of FPNS
Population	Inclusion Criteria
	• Patients aged ≥18 years with cancer who were taking regular ATC opioids • One to four episodes of moderate to severe BTP per day
	Exclusion Criteria
	• Uncontrolled or rapidly escalating pain, unstable condition, or rapid deterioration • Respiratory, cardiac, hepatic, renal, neurologic, or psychiatric comorbidities • history of alcohol or substance abuse • MAOI therapy
	• Randomized / mITT N = 83; Completed N = 76; 459 FPNS BTP episodes; 200 placebo BTP episodes • Safety population N = 113
Intervention	• Patients were titrated to an effective dose of 100 - 800µg during an open-label titration phase. • Patients randomized to a treatment sequence with 10 nasal spray bottles; 7 FPNS and 3 placebo. • Patients could take a maximum of four doses per day with at least four hours between doses. If adequate analgesia was not achieved within 30 minutes or another BTP episode occurred within 4 hours, patients were permitted to take their usual BTP medication. • PI and PR scores were recorded at 0, 5, 10, 15, 30, 45, and 60 minutes. • Patient satisfaction was graded on a scale of 1 (not satisfied) to 4 (very satisfied).

Results

Efficacy

- Significantly more BTP episodes treated with FPNS than placebo had a ≥1-point reduction in pain intensity across all time points (5 – 60 minutes) and a ≥2-point reduction at 10 – 60 minutes.

≥2-point (clinically meaningful) reduction in PI and SPID

	PI (% episodes)			SPID (% episodes)		
Min	FPNS	Placebo	NeNT	FPNS	Placebo	NeNT
5	13.1	11.5	62.5	--	--	--
10	32.9	24.5	11.9	41.0	30.0	9.1
15	50.8	32.0	5.3	62.7	45.0	5.6
30	65.8	40.0	3.9	76.3	56.0	4.9
45	70.8	45.5	4.0	85.4	61.0	4.1
60	76.3	48.5	3.6	89.1	65.5	4.2

- SPID was significantly better for FPNS-treated episodes at 10 – 60 minutes.
- Rescue medication was required in 9.4% of FPNS-treated episodes, vs. 20.0% or placebo-treated episodes (P<0.001).
- Overall patients satisfaction of FPNS was 2.63 at 30 minutes and 2.73 at 60 minutes, compared to 2.01 and 2.02, respectively, for placebo (P<0.0001)
- Satisfaction with speed of relief for FPNS was 2.64 at 30 minutes and 2.05 at 60 minutes, vs. 2.70 and 2.03, respectively, with placebo.

Safety

- More patients experienced treatment related AEs with FPNS (25.7%) than placebo (1.3%)
- The most commonly reported AEs included vomiting (10.6%), nausea (8.8%), and dizziness (8.0%).
- Severe treatment-related AEs of sweating and vomiting and noncardiac chest pain were reported for one patient each for FPNS.
- Eight (7.1%) patients and one (1.3%) patient left the study early due to AEs associated with FPNS and placebo, respectively.
- Nasal events were generally mild, with one reported to be moderate (nasal dryness) and one severe (epistaxis).

Author's Conclusion

FPNS was effective in treating BTP, was well tolerated, and well accepted by patients compared to placebo.

Critique

Jadad Score: 3

Citation

Portenoy RK, Raffaeli W, Torres LM et al. Long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray for breakthrough cancer pain in opioid-tolerant patients. *J Opioid Manag* 2010;6(5):319-28

Study Design/ Methodology

16-wk MC OL

Analyses – Primary Criteria for Evaluation

Adverse events (AEs), nasal tolerability
Consistency of effect – additional rescue medication use and FPNS dose change

Population

Inclusion Criteria

- Chronic cancer pain treated with > or = 60 mg/d oral morphine or equivalent
- 1-4 CBTP episodes per day

Safety = 403 patients; 356 entered treatment phase; 110 completed
42,227 BTP episodes

Intervention

- 16-weeks of FPNS treatment following dose titration

Results

Safety

	• 99 patients (24.6%) reported treatment-related AEs; most were mild or moderate and typical of opioids. • 61 patients (15.1%) reported serious AEs; 5 were considered related to study drug. • 80 deaths, 1 assessed as possibly related to study drug • No significant local nasal effects
	Efficacy
	• No additional rescue medication was required after 94% of FPNS-treated episodes. • More than 90% of patients required no increase in their initial dose of FPNS
Author's Conclusion	FPNS was associated with AEs, typical of opioids, with no evidence of nasal toxicity. A large proportion of BTCP episodes were treated with a single dose, and doses remained stable over the 4-month period.
Critique	Jadad Score: 1

Citation	Fallon M, Reale C, Davies A et al., on behalf of the Fentanyl Nasal Spray Study 044 Investigators Group. Efficacy and safety of fentanyl pectin nasal spray compared with immediate-release morphine sulfate tablets in the treatment of breakthrough cancer pain: a multicenter, randomized, controlled, double-blind, double-dummy multiple-crossover study. *J Support Oncol* 2011;9(6):224-31.
Study Design/ Methodology	MC, DB/DD, multiple CO, RCT – additional results of study reported by Fallon (2011) Screening (max. 10 d), OL Dose-titration (max. 14 d); DB/DD Treatment (min–max: 3–21 d), End-of-Treatment (1–14 d after last dose)
	Efficacy Analysis – Primary Criteria for Evaluation
	PID15 (patient-averaged scores, as opposed to episode-averaged scores)
Population	Inclusion Criteria
	• Histologically confirmed cancer diagnosis • Receiving ATC opioids equivalent to ≥ 60 mg/d OM • One to four BTP episodes per day Study sites were located in Europe and India.
	Exclusion Criteria
	• Rapidly escalating or uncontrolled background pain, or medically unstable • Hx of alcohol or substance abuse
	• Mean Age – 55.9 • N = 110 entered OL titration phase; Safety N = 106; Randomized N = 84; Completed N = 79; mITT Efficacy N = 79. 372 FPNS episodes, 368 IRMS episodes. Safety N = 106. •
Intervention	• FPNS was titrated to an effective dose of 100–800 mcg/episode during an open-label titration phase. Oral IRMS was dosed as one-sixth of the total daily oral morphine dose equivalent of the patients' ATC opioid medication. • During the DB/DD, up to 10 BTP episodes were treated (5 with FPNS and encapsulated placebo; and 5 with IRMS and nasal spray placebo). • PI (11-pt NRS) and PR (0 = None, 4 = Complete, NRS) were recorded at 0, 5, 10, 15, 30, 45, and 60 minutes; additional rescue medication within 60 min.

Results

Efficacy

- Pt-averaged PID15 (reduction in PI from 0 to 15 minutes) was significantly greater for FPNS vs. IRMS (mean ± SE): 3.02 ± 0.21 vs. 2.69 ± 0.18 ($p<0.05$).
- FPNS was superior to IRMS in pt-averaged PID scores at each time point from 15 through 60 min ($p<0.05$); PR at all points at 30–60 min ($p\leq0.005$); and mean differences in TOTPAR at all points from 15–60 min ($p<0.05$).
- FPNS was also statistically superior to IRMS in episode-averaged PID from 30 to 60 min ($p \leq 0.05$).
- Significantly more episodes treated with FPNS had a Clinically Meaningful Pain Relief (CMPR; ≥2-point or ≥33% reduction in PI) than with IRMS at 10 minutes (52.4% vs. 45.4%) and 15 minutes (75.5% vs. 69.3%) (both $P<0.05$). NSD between treatments at 5 minutes and from 30 minutes on.
- Significantly more episodes had a ≥2-point mean reductions in SPID score at 10 minutes after FPNS than after IRMS administration ($P < 0.05$)
- The number of episodes with a PR score of ≥2 was significantly higher in FPNS episodes than IRMS episodes at 15 and 30 minutes ($P<0.05$ and $P<0.0001$, respectively).
- Significantly more episodes achieved ≥33% reduction in PI with FPNS than IRMS at 10 minutes (33.9% vs. 28.3%; $p<0.0357$) and 15 minutes (55.4% vs. 47.3%; $p<0.0056$).
- Significantly more episodes achieved maximal PR (score of 4) with FPNS than IRMS at 45 minutes (31.1% vs. 21.5%; $p<0.01$) and 60 minutes (50.1% vs. 34.3%; $p<0.0001$). NeNT for maximal PR: 10 and 7, respectively.
- Rescue medication was required for 3.0% of episodes treated with FPNS and 3.8% treated with IRMS (NSD).

Percentage of Episodes with Clinically Meaningful Pain Reduction (≥ 2-point or ≥33% Reduction in Pain Intensity)

Min	FPNS	IRMS	P	NeNT
10	52.4	45.4	< 0.05	15
15	75.5	69.3	< 0.05	17

Percentage of Episodes with ≥33% Reduction in Pain Intensity

Min	FPNS	IRMS	P	NeNT
10	33.9	28.3	0.0357	18
15	55.4	47.3	0.0056	13

Safety

- More TEAEs occurred with FPNS than IRMS, and most were mild to moderate.
- Eight patients discontinued the study due to AEs: six after treatment with FPNS and two after treatment with IRMS.
- SAEs (n): 6 (12 events) after FPNS vs. 2 (2 events) after IRMS
- Deaths (n): 6 (3 during screening before tx; 2 during titration; 1 during DB/DD phase); results not reported by tx group. One death was assessed as possibly related to study drug (circulatory insufficiency, hypotension, anuria after last treatment with FPNS).
- Nasal tolerability: not reported by tx group; NSD.
-

Summary of TEAEs, n (%)

TEAE	FPNS100 (N = 105)	FPNS200 (N = 82)	FPNS400 (N = 60)	FPNS800 (N = 23)	IRMS
Any	25 (23.8)	15 (18.3)	20 (33.3)	8 (34.8)	13 (16.3)
Most Common (≥5% in Any Treatment Group)					
Vomiting	4 (3.8)	2 (2.4)	3 (5.0)	2 (8.7)	3 (3.8)
Somnolence	2 (1.9)	4 (4.9)	3 (5.0)	0 (0.0)	1 (1.3)
Nausea	1 (1.0)	1 (1.2)	2 (3.3)	2 (8.7)	1 (1.3)
Constipation	2 (1.9)	1 (1.2)	3 (5.0)	0 (0.0)	1 (1.3)

Author's Conclusion	FPNS is efficacious, safe, well tolerated in CBTP; delivered early, clinically meaningful reductions in pain that matched or exceeded the effect of IRMS, and more complete pain relief for the entire duration of CBTP episodes treated.
Critique	Jadad Score: 3 Funding: Archimedes Development, Ltd.

Citation	Davies A, Sitte T, Elsner F et al. Consistency of efficacy, patient acceptability, and nasal tolerability of fentanyl pectin nasal spray compared with immediate-release morphine sulfate in breakthrough cancer pain. *J Pain Symptom Manage* 2011;41(2):358-66.
Study Design/ Methodology	MC, DB/DD, multiple CO, RCT – same trial reported by Fallon (2011)
	Efficacy Analysis – Primary Criteria for Evaluation
	PID15
Population	Inclusion Criteria
	• Histologically confirmed cancer diagnosis • Receiving ATC opioids • One to four BTP episodes per day
	Exclusion Criteria
	• Rapidly escalating or uncontrolled background pain, or medically unstable
	• Mean Age – 55.9 • N = 110 entered study; N = 84 entered OL titration phase; 372 FPNS episodes, 368 IRMS episodes • Safety N = 106
Intervention	• FPNS was titrated during an open-label titration phase. Oral IRMS was dosed as one-sixth of the total daily oral morphine dose equivalent of the patients' ATC opioid medication. • During the DB/DD, 10 BTP episodes were treated (5 with FPNS and encapsulated placebo; give with IRMS and nasal spray placebo). • PI and PR were recorded at 0, 5, 10, 15, 30, 45, and 60 minutes.
Results	**Efficacy**
	• At 10 and 15 minutes, significantly more episodes treated with FPNS had a ≥2-point reduction in PI than with IRMS (P<0.05). • The number of episodes with a PR score of ≥2 was significantly higher in FPNS episodes than IRMS episodes at 15 and 30 minutes (P<0.05 and P<0.0001, respectively). • Significantly more patients achieved total pain relief ≥33% with FPNS than IRMS at 15, 30, 45, and 60 minutes. • Rescue medication was required for 3.0% of episodes treated with FPNS and 3.8% treated with IRMS.

Percentage of episodes with total pain relief ≥33%

Min	FPNS	IRMS	P	NeNT
10	38.0	32.6	NS	18.5
15	52.3	40.5	≤0.01	11.4
30	59.8	51.0	≤0.01	11.4
45	76.2	64.3	<0.001	8.4
60	83.4	74.9	<0.01	11.8

	Safety
	• Slightly more AEs occurred with FPNS than IRMS and most were mild to moderate. • Eight patients discontinued the study due to AEs: six after treatment with FPNS and two after treatment with IRMS.

Author's Conclusion	FPNS was well tolerated and provided analgesia in a more rapid manner than IRMS, making it more suitable to treat BTP.
Critique	Jadad Score: 4

Citation	Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *J Natl Cancer Inst* 1998;90(8):611-6
Study Design/ Methodology	MC, DB, PC, 10-period CO, RCT
	Efficacy Analysis – Primary Criteria for Evaluation
	PID and total pain relief
Population	Inclusion Criteria
	• Age 18 or older • Opioid tolerant • Relatively stable cancer pain
	Exclusion Criteria
	• History of psychiatric disease or drug abuse • Oral, hepatic, renal, or cognitive disease
	• Mean age – 54 • Sex – 55% female; 45% male • Race – 93% white; 5% black; 1% asian ATC opioids (%) – morphine (68); transdermal fentanyl (23); other (19). Supplemental opioids (%) – oxycodone (37); morphine (30); hydrocodone (13); hydromorphone (12); other (8). ITT N = 86
Intervention	OTFC lozenge titrated to an effective dose of 200-1600 µg during an open-label titration. Patients were randomized to a treatment sequence with 10 tablets; 7 OTFC lozenge and 3 placebo. Throughout the double-blind study, 804 BTP episodes were treated; 247 with placebo and 557 with OTFC lozenge. Patient were required to wait at least 2 hours between doses. If pain relief was not achieved within 30 minutes of study drug administration, patients were permitted to take a dose of their regular BTP medication. SPID, PR, PI, and global performance evaluation was assessed at 15, 30, 45, and 60 minutes post-dose.
Results	**Efficacy**

<table>
<tr><td></td><td>
• PID and PR were significantly better for OTFC lozenge than placebo at all time points (P<0.0001)
<table>
<tr><th></th><th colspan="4">PID</th><th colspan="4">PR</th></tr>
<tr><th></th><th colspan="8">Minutes</th></tr>
<tr><th>Treatment</th><th>15</th><th>30</th><th>45</th><th>60</th><th>15</th><th>30</th><th>45</th><th>60</th></tr>
<tr><td>OTFC lozenge</td><td>1.62</td><td>2.41</td><td>2.88</td><td>3.19</td><td>1.42</td><td>1.80</td><td>2.00</td><td>2.14</td></tr>
<tr><td>Placebo</td><td>1.02</td><td>1.51</td><td>1.91</td><td>2.13</td><td>0.93</td><td>1.11</td><td>1.30</td><td>1.33</td></tr>
</table>
• Mean global performance evaluation was 1.98 for OTFC lozenge and 1.19 for placebo (P<0.0001)
• More patients (34%) required rescue medication for BTP episodes treated with placebo than episodes treated with OTFC lozenge (15%) [relative risk = 2.27; P<0.0001)
</td></tr>
<tr><td></td><td>Safety</td></tr>
<tr><td></td><td>Adverse events occurring in ≥5% patients included dizziness (17), nausea (14), somnolence (8), constipation (5), and asthenia (5).</td></tr>
<tr><td>Author's Conclusion</td><td>OTFC appears effective in the treatment of cancer-related breakthrough pain.</td></tr>
<tr><td>Critique</td><td>Jadad Score: 4</td></tr>
</table>

<table>
<tr><td>Citation</td><td>Mercadante S, Villari P, Ferrera P, Casuccio A, Mangione S, Intravaia G. Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. Br J Cancer 2007;96(12):1828-33</td></tr>
<tr><td rowspan="2">Study Design/ Methodology</td><td>CO, RCT</td></tr>
<tr><td>Efficacy Analysis – Primary Criteria for Evaluation
SPID30</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria
• Adult cancer patients who were opioid tolerant.
• Having acceptable pain relief on current medications.
• Experiencing ≤2 BTP episodes per day.</td></tr>
<tr><td>Exclusion Criteria
• Patients <18 or >80 years of age.
• Patients with important metabolic alterations, cognitive failure, or lack of cooperation.
• Patients with short-lived episodic pain.</td></tr>
<tr><td>
• N = 25; 53 pairs episodes treated
• Mean Age – 59
• Sex – 12 male; 13 female

Dosage distribution across episode pairs treated
<table>
<tr><th>OTFC lozenge/IVMO Dose (mcg/mg)</th><th>Number of patients</th><th>Number of episode pairs treated</th></tr>
<tr><td>200/4</td><td>6</td><td>9</td></tr>
<tr><td>400/8</td><td>3</td><td>5</td></tr>
<tr><td>600/12</td><td>5</td><td>14</td></tr>
<tr><td>800/16</td><td>1</td><td>6</td></tr>
<tr><td>1200/24</td><td>8</td><td>13</td></tr>
<tr><td>1600/32</td><td>2</td><td>6</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>
• Patients were treated with a dose of each OTFC lozenge and IVMO for each pair of BTP episodes in randomized order with a washout period of at least 6 hours between treatments.
• For patients who repeated the treatment on another day, the medications were
</td></tr>
</table>

<table>
<tr><td></td><td>administered in the opposite order as the first day.
• OTFC lozenge and IVMO doses were calculated based on patients' ATC opioid dose.
• PI (scale 0 – 10) and opioid-related symptoms (scale 0 – 3; absent, slight, moderate, severe) were recorded by patients at 0, 15, and 30 minutes after study drug administration.
• A decrease in PI of ≥33% at 15 min post-dose, not requiring additional treatment within the next 2 hours, was considered an effective treatment for that episode.</td></tr>
<tr><td>Results</td><td>Efficacy
• PI scores were significantly better for IVMO at 15 post dose than OTFC lozenge, but not at 30 min post-dose (see table below).
• Three patients vs. one patient required additional rescue medication after treatment with OTFC lozenge and IVMO, respectively.
• There was no significant difference between the number of patients with a reduction of >33 and 50% at either time point (P=0.66 and 0.39 at 15 min and 0.23 and 0.2 at 30 min, respectively).

Mean reported PI at 0, 15, and 30 min post-dose
<table>
<tr><td></td><td>0 min</td><td>15min (% decrease from baseline)</td><td>30 min (% decrease from baseline)</td></tr>
<tr><td>OTFC lozenge</td><td>6.9</td><td>4.1 (41.4)</td><td>2.4 (65.9)</td></tr>
<tr><td>IVMO</td><td>6.9</td><td>3.3 (51.7)</td><td>1.7 (73.8)</td></tr>
<tr><td>P</td><td>N/A</td><td>0.013 (0.026)</td><td>0.059 (0.136)</td></tr>
</table>
Percentage of patients with >33 or 50% reduction at 15 and 30 min post-dose
<table>
<tr><td></td><td colspan="3">15 min post-dose</td><td colspan="3">30 min post-dose</td></tr>
<tr><td>Reduction in PI</td><td>OTFC lozenge</td><td>IVMO</td><td>NeNT</td><td>OTFC lozenge</td><td>IVMO</td><td>NeNT</td></tr>
<tr><td>>33%</td><td>57</td><td>74</td><td>5.9</td><td>85</td><td>87</td><td>50</td></tr>
<tr><td>>50%</td><td>38</td><td>55</td><td>5.9</td><td>75</td><td>75</td><td>N/A</td></tr>
</table>
Safety
AEs were mild and typical of opioid therapy, including nausea, drowsiness, and confusion.</td></tr>
<tr><td>Author's Conclusion</td><td>OTFC lozenge and IVMO were both effective at treating episodic pain, with the effects of IVMO being faster.</td></tr>
<tr><td>Critique</td><td>Jadad Score: 3</td></tr>
</table>

<table>
<tr><td>Citation</td><td>Coluzzi PH, Schwartzberg L, Conroy JD et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Pain 2001;91(1-2):123-30.</td></tr>
<tr><td>Study Design/ Methodology</td><td>MC DB DD Multiple CO RCT with open-label OTFC lozenge dose-titration phase followed by double-blind phase
mITT analysis; no imputation or deletion for primary efficacy outcome data
PI measured on 11-point numerical rating scale
Efficacy Analysis – Primary Criteria for Evaluation
PID15</td></tr>
<tr><td>Population</td><td>Inclusion Criteria
• Adults with 1–4 CBTP episodes per day while using a stable fixed schedule of oral opioid equivalent to 60–1000 mg of oral morphine per day or TD fentanyl 50–300 mcg/h.
• Using protocol-defined successful dose of 15, 30, 45, or 60 mg of MSIR for the target BTP (controlled for at least 3 days).
Exclusion Criteria</td></tr>
</table>

<table>
<tr><td></td><td>

Uncontrolled or rapidly escalating pain
Hypersensitivities, allergies, or contraindications
Recent history of substance abuse
Cardiopulmonary disease that would increase risk of potent opioids
Neurologic or psychiatric disease that would compromise data collection
Strontium 89 therapy in prior 60 days
Any therapy prior to study that could also pain or response to pain medication
Moderate or severe mucositis

</td></tr>
<tr><td></td><td>N = 134 enrolled, 93 (69%) successfully titrated on OTFC lozenge and randomized in DB phase; 84 completed; 75 evaluable for efficacy.
53% Male; mean (SD) age 55 ± 11 y; average daily pain 4.8 (SD 1.8, range 1–9); no significant baseline differences.</td></tr>
<tr><td>Intervention</td><td>OL Titration Phase: median of 2 doses of OTFC lozenge (range, 0–9) and a titration period of 5 days (range, 1–22; mode 3) were required before successful dose was found.

Double-blind Phase:
OTFC lozenge at dose determined to be successful in the OL titration phase (mean ± SD, 811 ± 452 mcg) vs. MSIR capsule at previously established successful dose (31.0 ± 13.5 mg)
Treatment continued until all 10 sets of study medication were taken or until 14 days elapsed.
Usual MSIR doses could be used for nontarget BTP</td></tr>
<tr><td>Results</td><td>Efficacy</td></tr>
<tr><td></td><td>For the mITT population, mean PI was significantly lower with OTFC lozenge than MSIR at each time point (15–60 min; p ≤ 0.019).
Mean PR scores were significantly higher on OTFC lozenge than MSIR at each time point (p ≤ 0.011).

Efficacy Outcome Measures
<table>
<tr><th>Measure</th><th>OTFC lozenge</th><th>MSIR</th><th>NeNT</th></tr>
<tr><td>PID15 score, mean†</td><td>1.8*</td><td>1.4</td><td></td></tr>
<tr><td>PID >33% at 15 min, % of episodes</td><td>42.3**</td><td>31.8</td><td>10</td></tr>
<tr><td>Global medication performance rating, mean</td><td>2.5**</td><td>2.1</td><td></td></tr>
<tr><td>Pt required additional medication, % of episodes</td><td>2</td><td>1</td><td></td></tr>
<tr><td colspan="4">*p ≤ 0.008
**p < 0.001
† Estimated from Figure 4 of article</td></tr>
</table>
</td></tr>
<tr><td></td><td>Safety</td></tr>
</table>

<table>
<tr><td></td><td>

Attribution of AEs to study treatment was difficult because of the study design (patients were receiving ATC opioids, OTFC lozenge, and MSIR during the DB phase).
Most AEs were considered unrelated or unlikely to be related to study medication common AEs were generally mild to moderate in intensity.
None of 9 deaths that occurred during or following the study were attributed to study medication.
Six of 18 patients had WDAEs considered at least possibly related to study medication: 5 withdrew because of nausea, vomiting, sedation, and dizziness; one withdrew because of hospitalization for intractable pain, hallucinations, and confusion (considered probably related to study drug) during OTFC lozenge titration.

Safety Measures (n, %)
<table>
<tr><td>Measure</td><td>Overall (N = 93)</td></tr>
<tr><td>Deaths</td><td>9</td></tr>
<tr><td>SAEs</td><td>NR</td></tr>
<tr><td>WDAE</td><td>18 (13)</td></tr>
<tr><td>≥ 1 AE</td><td>NR</td></tr>
</table>
Common AEs (n, %)
<table>
<tr><td>AE</td><td>Overall (N = 134)</td></tr>
<tr><td>Somnolence</td><td>20 (15)</td></tr>
<tr><td>Constipation</td><td>14 (10)</td></tr>
<tr><td>Dizziness</td><td>10 (7)</td></tr>
</table>
</td></tr>
<tr><td>Author's Conclusion</td><td>OTFC lozenge was superior to MSIR and offers an effective alternative to oral morphine.</td></tr>
<tr><td>Critique</td><td>Jadad score = 5; adequate allocation concealment
Supported by a grant from Anesta Corp., which became a subsidiary of Cephalon in October 2000.</td></tr>
</table>

Systematic Review of INFS (INSTANYL®) Versus Other Fentanyl TM IR and Morphine in CBTP

<table>
<tr><td>Citation</td><td>Vissers D, Stam W, Nolte T, Lenre M, Jansen J. Efficacy of intranasal fentanyl spray versus other opioids for breakthrough pain in cancer. Curr Med Res Opin 2010;26(5):1037-45</td></tr>
<tr><td>Study Design/ Methodology</td><td>Systematic Review
Pooled data using a fixed-effect Bayesian mixed-treatment comparison model. Since trials assessed PI at different time points, a proxy for "missing" data was calculated by averaging PIDs from adjacent time points.
Reported 95% Credible Intervals (95% CrI), "reflecting the range of true underlying effects with 95% probability to summarise the posterior distribution of the treatment effects. CrI instead of confidence interval were used to differentiate the uncertainty obtained with a Bayesian approach from that obtained with a frequentist approach. The main difference between 95% CI and 95% CrI is that the latter can be interpreted in terms of the 95% probability that the true (or population) value is between the boundaries of the interval, whereas a confidence interval cannot be interpreted in this way."
Sensitivity analysis to assess the impact of a single trial (Mercadante 2009) on pooled results.</td></tr>
<tr><td></td><td>Efficacy Analysis – Primary Criteria for Evaluation</td></tr>
<tr><td></td><td>PID</td></tr>
</table>

Population

Inclusion Criteria

- Any RCT comparing oral morphine (OM), INFS, FB tablet, and/or OTFC lozenge in the management of cancer BTP.
- Adult cancer patients suffering from BTP.
- Outcome measures of PID.

Study Features

- Included 6 DB RCTs; N=594 patients, range 86 to 139.
- Four were PC studies evaluating OTFC lozenge (Farrar 1998), INFS (Kress 2009), and FB tablet (Portenoy 2006; Slatkin 2007).
- One trial compared OTFC lozenge with OM (Coluzzi 2001).
- One trial compared INFS with OTFC lozenge (Mercadante 2009).
- Each study began with an open-label dose titration phase.
- Studies were randomized with a crossover design.

Results

Efficacy

- The authors report that there is more than 99% probability that INFS provides the greatest PR within 15 minutes.
- For INFS, PID on 11-point numerical rating scale at 15, 30, 45, and 60 minutes was 1.7 points (95% CrI 1.4–1.9), 2.0 (1.6–2.3), 2.0 (1.5–2.4) and 1.9 (1.5–2.4), respectively.
- Differences in PID favoring INFS were 1.2 points (95% CrI: 0.8; 1.5) relative to FBT, 1.3 (0.9; 1.6) points relative to OTFC and 1.7 (1.1; 2.3) points relative to OM.
- OM did not show a significant benefit over placebo until 45 minutes post-dose.
- Based on indirect comparisons, INFS seemed to achieve earlier and greater pain reduction, showing statistically significant differences relative to FB tablet at 15 and 30 minutes; OTFC lozenge at 15, 30, and 45 minutes, and OM at all time points 15-60 minutes.

Mean PID of study medications at various time points from reviewed articles

	Mean PID				
Minutes	**Placebo**	**INFS**	**OTFC LOZENGE**	**FB TABLET**	**OM**
10	1.28 0.50	2.56 2.39	1.10	0.90	--
15	0.48 1.02 0.80	3.39	1.62 1.86 1.96	0.93 1.39	1.44
20	2.02	3.92 4.06	2.78	--	--
30	1.40 1.51 1.29	4.54	2.41 2.88 3.69	2.30 2.29	2.39
40	2.28	4.37			
45	1.89 1.91 1.43	--	2.88 3.52	3.27 2.86	3.03
60	2.46 2.26 2.13 1.55	4.57 4.98	4.73 3.19 4.02	3.96 3.21	3.52

Author's Conclusion	INFS provided the fastest pain relief and continued to provide analgesia throughout most of the episode. INFS is superior to the other BTP treatments compared. Because of a slow onset of effect, oral morphine could not be considered an appropriate treatment for breakthrough cancer pain. The authors suggested that where BTCP pain peaks within minutes, intranasal fentanyl spray should be administered as the optimal treatment.
Critique	FAIR quality. Clearly reported research question and results; appropriate study selection criteria; relevant databases; no date or language restrictions; included unpublished studies but only for INFS. Unclear how many reviewers performed the study selection and data extraction (potential for reviewer error and bias), although a second reviewer checked the data. Quality assessment of included studies was not stated, although some elements of quality were mentioned (e.g., randomization, blinding) and only RCTs were eligible for inclusion. Unclear whether sensitivity analysis was planned a priori. Lacked sensitivity analyses to evaluate effects of trial quality and heterogeneity in outcomes. Sufficient trial details were reported; method of synthesis appeared appropriate but was somewhat novel. The adjusted PID values in the report by Mercadante (2009)[21] were lower than the (unadjusted?) PID values reported for the same study in this systematic review for both INFS (by 0.14 to 0.48 points) and OTFC lozenge (by 0 to 0.33 points. An opposite pattern, with slightly higher PID values in the original report than those in this systematic review, occurred with the study by Farrar (1998).[20] These discrepancies would probably not substantially affect the overall relative results of the systematic review; however, the reasons for these discrepancies were not explained. Overall, results seemed reliable and the authors' conclusion was supported by the results. COI: All authors disclosed financial interest or employment with Nycomed (manufacturer of INFS).

Summary of Trials Evaluating Transmucosal Immediate-release Fentanyl in Indications Other than CBTP

<table>
<tr><td>Citation</td><td>Darwish (2007); FB tablet and Mucositis</td></tr>
<tr><td>Study Design/ Methodology</td><td>Phase I, MC, OL</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td></tr>
<tr><td>• Patients ≥18 years who were opioid tolerant
• Mucositis (if present) of grade 1-3 upon clinical exam and grade 1-2 upon functional/symptomatic exam
• Agreement to withhold topical treatment for mucositis between 1 hour before and up to 8 hours after FB tablet administration</td></tr>
<tr><td>Exclusion Criteria</td></tr>
<tr><td>• Pregnancy
• Use of oral contraceptives within past 2 weeks
• Active brain metastases, increased intracranial pressure, COPD, risk of significant bradycardia

<table>
<tr><th></th><th>Patients w/ mucositis (n=8)</th><th>Patients w/o mucositis (n=8)</th></tr>
<tr><td>Age (median)</td><td>62.5</td><td>50.5</td></tr>
<tr><td>Male (%)</td><td>13</td><td>50</td></tr>
<tr><td>Female (%)</td><td>88</td><td>50</td></tr>
<tr><td>White (%)</td><td>38</td><td>100</td></tr>
<tr><td>Black (%)</td><td>63</td><td>0</td></tr>
<tr><td>BMI (Median)</td><td>27.9</td><td>29.4</td></tr>
</table>
The clinical grade for mucositis was 1 in all eight patients; the functional grade was 1 in 7 patients and 2 for one patient.</td></tr>
<tr><td>Intervention</td><td>Patients self-administered a 200 µg dose. Patients with mucositis placed FB tablet in the least affected buccal area (but not in a non-affected area).</td></tr>
</table>

<table>
<tr><td></td><td>Fentanyl concentrations were measured from venous blood samples immediately prior to and 10, 20, 30, 40, 45, and 50 minutes and 1, 2, 3, 4, 6, and 8 hours after FB tablet placement.</td></tr>
<tr><td rowspan="3">Results</td><td>Efficacy</td></tr>
<tr><td>No statistically significance was observed between patients with mucositis and without mucositis in any pharmacokinetic parameters.
<table>
<tr><td></td><td>W/ mucositis (median)</td><td>W/O mucositis (median)</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>1.14</td><td>1.21</td></tr>
<tr><td>AUC_{tmax} (ng • h/mL)</td><td>0.17</td><td>0.20</td></tr>
<tr><td>T_{max} (min)</td><td>25.0</td><td>22.5</td></tr>
</table></td></tr>
<tr><td>Safety</td></tr>
<tr><td></td><td>Nausea, back, pain, anaemia, and dizziness were experienced each in one patient without mucositis. One patient with mucositis reported dizziness. No significant AEs were observed in either group. No changes in oral mucosa were observed for up to 8 hours after FB tablet administration.</td></tr>
<tr><td>Author's Conclusion</td><td>Mucositis does not appear to affect the absorption or FB tablet and dose adjustments are not needed in patients with mucositis, though further studies may be warranted.</td></tr>
<tr><td>Critique</td><td>Jadad Score: N/A</td></tr>
</table>

<table>
<tr><td>Citation</td><td>Shaiova (2004): Mucositis and oral transmucosal fentanyl lozenge</td></tr>
<tr><td rowspan="3">Study Design/ Methodology</td><td>DB, CO, RCT</td></tr>
<tr><td>Efficacy Analysis – Criteria for Evaluation</td></tr>
<tr><td>• Oral mucositis grade (0=none, 1=erythema of the mucosa, 2=patchy pseudomembranous reaction, 3=confluen pseudomembranous reaction, 4=necrosis or deep ulceration).
• Tolerability on a 4-point scale
<table>
<tr><td>1</td><td>Easily tolerated, no discomfort with use</td></tr>
<tr><td>2</td><td>Mild discomfort with use, but not enough to interfere with administration</td></tr>
<tr><td>3</td><td>Moderate discomfort with use, administration somewhat impaired</td></tr>
<tr><td>4</td><td>Severe discomfort, unable to administer unit</td></tr>
</table>
• Pain on a 100 mm VAS
• Administration time
• Formulation preference</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td></tr>
<tr><td>• Patients with radiation-induced grade 3 or 4 oral mucositis.
• Receiving ATC opioids for at least 1 week, with a stable dose for at least 48 hours.
• Oral mucositis pain score of at least 33 mm on a VAS ranging from 0 to 100 mm.</td></tr>
<tr><td>Exclusion Criteria</td></tr>
<tr><td></td><td>• Use of local analgesics for oral mucositis that may affect fentanyl tolerability.
• History of substance abuse.
• Cardiopulmonary, neurologic, or psychiatric disease that could compromise data collection.
• Participation in clinical drug study within past 30 days.</td></tr>
<tr><td></td><td>• N = 14
• Mean Age – 53
• Sex – 29% female; 71% male
• Race – 79% white; 7% black; 7% Hispanic; 7% other
• Oral mucositis grade – 3(86%); 4(14%)</td></tr>
</table>

Intervention	• Each patient received a dose of oral transmucosal fentanyl before each of four visits for radiation treatments; two units of a sweetened matrix and two units of a compressed powder formulation. • For each formulation, one dose contained 200 mcg fentanyl and one contained placebo. • Each dose was separated by at least 16 hours. A minimum of 2 hours must have passed between the last usage of a patient's usual analgesic and administration of the study drug. • After administration of the study drug, mucositis pain was scored at 5, 10, 15, 30, and 45 minutes. • Vital signs were measured at 0, 15, 30, and 45 minutes. • When patients indicated they were finished with the study drug, the time was recorded, oral mucosa examined, and the investigator estimated the amount of study drug consumed.
Results	**Efficacy**
	• More patients considered the sweetened matrix to be easily tolerated than the compressed powder (93% vs. 62%), but this difference was not statistically significant (P=0.063). • Mean VAS scores did not vary significantly between formulations (P = 0.146 within active formulations and P = 0.186 within placebo), nor did they vary much between fentanyl and placebo (-30 vs. -45 for sweetened matrix and -40 vs. -32 for compressed powder, respectively). • Mean time to maximum change in VAS, percent consumption, and administration time did not vary significantly between formulations (P=0.207, 0.125, and 0.445 respectively). • Seven patients (50%) preferred the sweetened matrix, three (21%) preferred compressed powder, and 3 (21%) had no preference. This difference was not significant (P=0.343).
	Safety
	• No changes in oral mucosa were observed. • The most common AE reported was a burning sensation at application site (7 patients).
Author's Conclusion	Both the sweetened matrix and compressed powder formulation of oral transmucosal fentanyl were well tolerated in patients with severe mucositis.
Critique	N/A