

Review of Fentanyl Effervescent Buccal Tablets (Fentora[®], Cephalon, Inc.)

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The incidence of breakthrough pain (BTP) in cancer patients utilizing continuous opioid therapy has been consistently reported as greater than 60% in most studies.¹ The incidence of cancer breakthrough pain has been reported to increase with the severity of disease. Studies have shown that chronic pain patients who experience BTP utilize the emergency department 2.5 times more often and utilize 44% more in pain-related costs than chronic pain patients without breakthrough pain.² Additionally, breakthrough pain accounts for greater than 4% of all hospital re-admissions.

Current literature delineates three types of breakthrough pain. *End-of-dose failure* breakthrough pain is precipitated by decreasing serum concentrations of long-acting opioid therapy prior to the next scheduled dose.^{1,3} *Incidental* breakthrough pain is associated with an event such as walking or getting out of a chair and can be classified as anticipated or unanticipated. And *spontaneous* breakthrough pain is characterized by its lack of a recognizable precipitating factor such as intense bone pain while sitting motionless. The time from onset of breakthrough pain until maximum intensity is highly variable, but is generally expected to be within one hour. Currently accepted cancer pain treatment guidelines recommend dose titration with any short-acting oral opioid therapy for BTP in an opioid-tolerant patient.⁴

Currently available treatment options include two rapid acting oral transmucosal fentanyl formulations. An oral transmucosal "lollipop" formulation (Actiq[®], Cephalon, Inc.) has been utilized for the treatment of breakthrough cancer pain since receiving FDA approval in 1998. The second transmucosal fentanyl formulation to be brought to market, the fentanyl citrate effervescent buccal tablet (Fentora[®], Cephalon, Inc.), was FDA approved in September 2006 for the treatment of BTP in cancer patients. The role of transmucosal fentanyl formulations in the treatment of BTP is reviewed here.

PHARMACOLOGY

Fentanyl is a pure mu opioid receptor agonist.⁵ The primary therapeutic effect of fentanyl is analgesia produced by mu opioid receptor activation in the CNS. Fentanyl is 70-100 times more potent in analgesic effect than morphine, most likely due to its rapid penetration into the CNS. The analgesic effects of fentanyl are subject to highly variable patient-specific factors and the level of opioid tolerance that exists in the patient. Fentanyl penetrates the CNS within three to five minutes after absorption and the analgesic effects increase with increasing doses. The maximum dose is limited only by side effects such as somnolence and respiratory depression. Other effects of pure opioid agonists include anxiolysis, euphoria, feelings of relaxation, constipation, miosis and cough suppression.

PHARMACOKINETICS

Fentanyl citrate molecules are poorly absorbed through the oral mucosa unless they are in solution in an alkaline environment.⁷ However, to be readily incorporated into solution, fentanyl citrate must be in an acidic environment. Upon administration of fentanyl tablets, effervescent activity creates an acidic environment around the tablet causing fentanyl to be dissolved into solution. As the tablet continues to dissolve, sodium bicarbonate is released increasing the pH of the nearby mucosa and allowing for maximal drug absorption. This process results in absorption of 50% of the active drug transmucosally. If any tablet remains after 30 minutes, it is swallowed with a glass of water and is subjected to slower, less extensive absorption by the intestinal mucosa.⁵ The absolute bioavailability of fentanyl in the FEBT formulation is 65%, compared to 47% for the oral transmucosal fentanyl citrate (OTFC) "lollipop" formulation. Fentanyl effervescent buccal tablets reach a C_{max} of 1.02 ng/mL (compared to 0.63 ng/mL for OTFC) and reach C_{max} at a median time of 46 minutes, compared to 91 minutes for OTFC. Maximum serum fentanyl concentrations increase proportionally with increasing

TABLE 1. SELECTED IMMEDIATE-RELEASE OPIOID FORMULATION PHARMACOKINETICS

Opioid	Onset of analgesia	Tmax	Elimination half-life
Morphine (oral)	30 – 40 minutes	1 hour	1.5 – 4.5 hours
Oxycodone (oral)	30 minutes	1.6 hours	3.2 hours for 20 mg dose
Hydromorphone (oral)	30 minutes	0.8 – 1 hour	2.5 hours
Methadone (oral)	10 – 15 minutes	2 – 4 hours	23 hours
Fentanyl (transmucosal)	10 – 15 minutes	1.5 hours	7 hours
Fentanyl (buccal)	10 – 15 minutes	0.75 hours	2.6 – 11.7 hours (dose dependent)

Data obtained from Micromedex[®] Healthcare Series.⁸

FEBT doses from 100-800 mcg, with doses greater than 800 mcg showing a 20% less than expected increase in the C_{max} .^{5,7} Transmucosal administration of fentanyl bypasses first-pass metabolism in the liver. Fentanyl is 80-85% protein-bound and distributes freely into the CNS within three to five minutes of absorption due to its highly lipophilic structure.⁵ Fentanyl undergoes metabolism to norfentanyl in the liver and intestinal mucosa by the CYP450 3A4. Norfentanyl has not demonstrated activity. Elimination occurs primarily in the urine in the form of N-dealkylated and hydroxylated metabolites (greater than 90%) and unchanged drug (7%). The median elimination half-life increases with increasing doses, ranging from 2.63 to 11.70 hours. See Table 1 for a comparison of pharmacokinetic parameters of short-acting opioid formulations for BTP.

PUBLISHED CLINICAL STUDIES

Evaluation of Pain rating scales in studies

One of the most common pain rating scales used in studies is the pain intensity (PI) scale. This 11-point scale ranges from 0 = no pain to 10 = worst pain imaginable. The minimum clinically important change (MCIC) in PI has been evaluated in several studies.^{9,10} However, no studies to date have evaluated MCIC in PI in breakthrough cancer pain. A review article comparing the study design and methods of similar PI scale evaluation trials concluded that a change of 3.5 points on the PI scale in the setting of acute pain would indicate a MCIC.¹¹

The pain relief (PR) scale was used as a secondary outcome measure in both FEBT trials. This 5-point scale ranged from 0 = none to 4 = complete relief. The global medication performance scale (GMP) was also evaluated in the FEBT trials. This scale included 5 points ranging from 0 = poor to 4 = excellent performance. The GMP scale (or a similar scale) is often included in pain studies to act as a comparator to the PI scale to ensure that the change in PI measured is meaningful to the patients being treated.^{9,11}

Breakthrough Cancer Pain

Portenoy et al. conducted a double-blind, randomized, multicenter, placebo-controlled study to evaluate the efficacy, safety and tolerability of FEBT in the treatment of breakthrough cancer pain in opioid-tolerant patients.¹² The primary outcome measure was the pain intensity difference (PID) score at 30 minutes post-intervention. The secondary measures included PID scores at all time points, pain relief (PR) scores, sum of pain intensity difference (SPID) scores, total pain relief (TOTPAR) scores, and global medication performance (GMP) scores.

Study participants included individuals greater than or equal to 18 years of age currently receiving 60 to 1000 mg oral morphine equivalents daily (or 50 to 300 mcg transdermal fentanyl per hour for longer than one week) and experiencing 1-4 BTP episodes per day. Participants had to have a solid or hematologic malignancy as the primary source of pain and their BTP had to have been successfully treated with a single short-acting oral opioid regimen. Study participants utilizing intrathecal opioids were excluded. Any patients with oral mucosal alterations that could affect tolerability or absorption of FEBT were also excluded. In accordance with prescribing information, pregnant or lactating patients or patients who had sleep apnea, brain metastases with

increased intracranial pressure, chronic obstructive pulmonary disorder, underlying bradyarrhythmia, or impaired renal or hepatic function were excluded.

Potential study participants were screened and initiated on a FEBT dose-titration protocol. Fentanyl buccal tablets were provided to participants in 100, 200, 400, 600 and 800 mcg doses. They were instructed to take a 100 mcg tablet at the first sign of a BTP episode and were monitored for efficacy and adverse effects. If the dose was ineffective but tolerated, the participant would increase to the next tablet strength at the onset of the next BTP episode (more than four hours after the last). Participants were allowed to use their pre-trial rescue opioid regimen between BTP episodes for resistant pain.

Participants tolerating two consecutive successful BTP treatments with FEBT doses of 800 mcg or less were randomized. They were given seven FEBTs and three placebo tablets in a randomly assigned order to be taken sequentially over the course of 10 BTP episodes within the following 21 days. Patients were also allowed to continue their pre-trial short-acting oral rescue opioid if needed for any BTP episode not responding to FEBT treatment within 30 minutes, any BTP episode occurring within 4 hours of the last FEBT dose, or for more than 4 BTP episodes per day. Participants were told to report baseline PI scores; 15-, 30-, 45- and 60-minute post-FEBT administration PI and PR scores; and 30- and 60-minute GMP scores. Adverse event reporting was allowed and assessed.

Of the 123 patients enrolled in the titration phase of the study, 77 were randomized to one of the treatment schedules. The primary outcome measure, PID for FEBT at 30 minutes, was 2.3 compared to 1.4 for the placebo ($p \leq 0.0001$). All secondary measures were significantly improved for FEBT over placebo at all time points (values were only represented graphically). The GMP scores were significantly improved for FEBT over placebo at 1.4 compared to 0.9 at 30 minutes ($p \leq 0.0001$) and 2.1 compared to 1.3 at 60 minutes ($p \leq 0.0001$). A greater number of BTP episodes treated with FEBT resulted in improvement in PI scores by 33% at all time points ($p \leq 0.05$) and 50% beyond 30 minutes ($p \leq 0.05$) over placebo-treated BTP episodes. The authors indicated that the study yielded >95% power to detect a difference of 1.4 in the PI scale. The authors did not comment on the statistical power required for the secondary outcomes. The results of this study did not achieve the MCIC of 3.5 between FEBT and placebo described for the PI scale in previous studies. The changes in GMP scores between FEBT and placebo, although statistically different, were not substantial enough to increase patient perception of medication performance by a single point on the scale. The type and rate of adverse effects reported were similar to expectations for opioid treatment with the exception of a 2% study withdrawal rate for FEBT application site ulcers.

Breakthrough Low Back Pain

A second study from Portenoy et al. compared FEBT to placebo for the treatment of breakthrough pain in patients with chronic low back pain stabilized on continuous opioid therapy.¹³ This randomized, double-blind, placebo-controlled, 16-center trial incorporated an open-label titration phase prior to randomization. The primary outcome measure in this study was the sum of

PI differences from five through 60 minutes (SPID₆₀). Secondary outcome measures included the PI differences and PR scores at all other time points and time to “meaningful” pain relief as defined by the patient. Additional analyses that served as secondary measures included a comparison of BTP episodes with >33% and >50% improvement in PI scores for FEFT versus placebo, a comparison of the number of BTP episodes in which “meaningful” pain relief was achieved for FEFT versus placebo, and a comparison of the number of BTP episodes requiring the use of a supplemental medication for FEFT versus placebo.

Study participants included individuals 18 to 80 years of age currently receiving >60 mg oral morphine equivalents daily (or >25 mcg/hr transdermal fentanyl) for longer than one week and experiencing 1-4 BTP episodes per day that were somewhat effectively treated with short-acting opioid therapy. The average daily PI score required for inclusion into the study was >6 for the 24 hours preceding consent with BTP episodes of <4 hours duration each. Participants had to have a diagnosis of chronic low back pain associated with osteoarthritis, degenerative disc disease, or spondylolisthesis (or other conditions with special permission) causing three months of functional disability. In accordance with prescribing information, pregnant or lactating patients were excluded. Patients with allergy or contraindication to any component of the study medication were excluded. Other exclusion criteria included rapidly escalating or uncontrolled pain, cardiopulmonary conditions unsafe for opioid use, medical or psychiatric illness (including alcohol or substance abuse within the last five years) that would compromise data collection, and scheduled surgeries during the study period.

Potential study participants were screened and initiated on a FEFT dose-titration protocol. Fentanyl buccal tablets were provided to participants in 100, 200, 400, 600 and 800 mcg doses. They were instructed to take a 100 mcg tablet at the first sign of a BTP episode. If patients did not experience pain relief within 30 minutes they were allowed to take a second 100 mcg dose. If the dose was ineffective but tolerated in two out of three consecutive BTP episodes, the participant would increase to the next tablet strength at the onset of the next BTP episode (more than two hours after the last). Titration proceeded in this fashion until BTP was adequately treated or the 800 mcg dose was deemed ineffective. Participants were allowed to use their pre-trial rescue opioid regimen between BTP episodes for resistant pain.

If successfully titrated to an available FEFT dose, participants were randomized to one of three different double-blinded BTP dosing sequences. Each contained six active FEFT doses (individualized to each patient’s effectively titrated dose) and three placebo tablets to treat nine consecutive episodes of BTP within the following three weeks. Pain intensity and PR were measured at 5, 10, 15, 30, 45, 60, 90, and 120 minutes after administration. Additionally, patients were asked to document at which time point they first felt “meaningful” pain relief.

Of the 105 patients enrolled in the titration phase of the study, 77 were randomized to one of the treatment schedules. For the primary outcome measure (SPID₆₀), FEFT showed statistically significant improvement over placebo; 8.3 vs. 3.6 ($p < 0.0001$), respectively. The authors deemed a difference in SPID₆₀ of three to be clinically relevant; however, the basis for

this conclusion was not described. The study yielded a power of 90-94% to detect that difference. Fentanyl effervescent buccal tablets demonstrated statistically significant benefits over placebo for most secondary endpoints including PI scores at each time point starting at ten minutes ($p < 0.0001$), PR scores at each time point starting at 15 minutes ($p < 0.0001$), a greater proportion of patients experiencing “meaningful” BTP relief (70% vs. 30%, $p < 0.0001$), a greater proportion of patients experiencing “meaningful” PR at 30 minutes (38% vs. 16%, $p < 0.0001$), a greater proportion of PI scores improved by >33% starting at 15 minutes (20% vs. 11%, $p < 0.01$) and >50% starting at 30 minutes (30% vs. 13%, $p < 0.0001$), and a smaller proportion of BTP episodes requiring supplemental treatment (16% vs. 46%, odds ratio, 0.22; 95% CI 0.13, 0.35). Adverse effects reported in this study were generally consistent with the type and frequency normally reported for opioid therapy. Exceptions to this were reports of dysgeusia in 8% of patients due to the taste of the FEFT, application site reactions including an ulcer at the application site in one patient, and one accidental overdose without explanation (four 600 mcg tablets taken at one time) requiring resuscitation and hospitalization.

DRUG INTERACTIONS

When administered with other CNS depressant medications (other opioids, sedatives, hypnotics, anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines and alcohol) depressant effects could be markedly increased leading to excessive sedation, hypoventilation and hypotension.⁵ Fentanyl should not be used within 14 days of monoamine oxidase inhibitor therapy.

One randomized crossover study suggests that ritonavir may decrease the clearance of fentanyl by 67% resulting in a 174% increase in AUC_{0-∞}.¹⁵ Potent and mild inhibitors of CYP450-3A4 (ketoconazole, itraconazole, clarithromycin, nelfinavir, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil and grapefruit juice) have been shown to increase fentanyl plasma concentrations leading to toxicity and excessive CNS depressant effects.^{5, 15}

ADVERSE EFFECTS AND PRECAUTIONS

Adverse effects reported in clinical trials were similar to other opioid therapies.^{3, 5, 12} Adverse effects for FEFT were evaluated in opioid-tolerant patients during concomitant use of chronic long-acting opioid therapy. The most common adverse effects in this setting were nausea, vomiting, constipation, asthenia, peripheral edema, fatigue, headache, dizziness, dehydration and anemia.

Evidence comparing FEFT adverse effects to other BTP treatment regimens has not been published. The adverse effects of fentanyl may differ from other opioid agonist and agonist/antagonist therapies.¹⁶ Opioid agonists may inhibit the secretion of ACTH, cortisol, and luteinizing hormone.⁵ An increased secretion of prolactin, growth hormone, insulin, and glucagon has been seen. Opioids have shown a variable effect on the release of thyroid stimulating hormone. Opioid agonists can promote the release of histamine possibly leading to pruritus, red eyes, sweating, and orthostatic hypotension. In contrast to most opioid therapies, fentanyl and its analogues do not cause histamine

release and fentanyl had less substantial effects as a myocardial depressant, leading to a comparatively lower incidence of bradycardia.¹⁶ One study reported erythema at the site of buccal tablet administration in 50% of patients.¹⁷ Less than 2% of patients have withdrawn from studies due to oral ulcers at the buccal tablet administration site.³ In comparison, current OTFC formulations are reported to cause dental caries at an unpredictable frequency according to evidence from case reports.¹⁸

Fentanyl effervescent buccal tablets carry a black box warning against use in non-opioid-tolerant patients (with opioid tolerance defined as use of any of the following for greater than one week: oral morphine 60 mg/day, transdermal fentanyl 25 mcg/hr, oxycodone 30 mg daily, oral hydromorphone 8 mg daily, or an equianalgesic dose of another opioid), postoperative pain, and children.⁵ The amount of fentanyl contained in one FEBT can be fatal to children. Great care should be taken to restrict the access of this medication to children. Fentora[®] is not supplied by the manufacturer in child-proof packaging. Care should be used when prescribing and dispensing transmucosal fentanyl formulations to ensure that the prescription clearly differentiates fentanyl *effervescent* buccal tablets from the OTFC formulation. The two products are not dose-equivalent and dispensing the wrong product could result in severe over- or under-dosing of the potent narcotic analgesic.

Fentanyl is a Schedule II narcotic. As with other potent opioid analgesics, fentanyl buccal tablets have a high potential for abuse and addiction.⁵ Patients should be monitored for signs of compulsive use, impaired control over drug use, continued use despite harm, and craving. Fentanyl may be abused without the presence of addiction or diverted for sale or use in combination with other psychoactive substances.

During titration to determine the most effective dose of FEBT, patients should possess only one strength of FEBT at a time due to the risk of accidental overdosing on a higher strength tablet. Up to four FEBT can be administered at one time to aid in dose titration without dispensing a new tablet strength. Patients should receive the single-tablet titrated dose after titration is complete.

Opioid analgesics can cause physical dependence. Physical dependence generally occurs after several weeks of continuous therapy. Patients with physical opioid dependence may experience withdrawal if therapy is abruptly discontinued.

As with all CNS depressant medications, patients should be cautioned against performing activities that require a high level of attention. Dangerous tasks such as operating heavy machinery and driving should be avoided.

The presence of several disease states warrant caution with concurrent use of opioid analgesics. Patients with chronic obstructive pulmonary disease are predisposed to respiratory depression caused by opioid analgesics. The clinical course of patients with head injury may be obscured by the effects of opioid analgesics. Patients with increased intracranial pressure or impaired consciousness may be susceptible to the effects of increased intracranial CO₂ retention caused by opioid analgesics.⁵ Patients with underlying cardiac disease may be more susceptible to bradycardia while taking opioid analgesics. Although evidence is lacking, caution should be used in patients with impaired hepatic or renal function due to the potential for increased plasma concentrations and accumulation.

TABLE 2. DOSING CONVERSION RECOMMENDATIONS

Currently available Actiq [®] (OTFC) Doses (mcg)	Currently available Fentora [®] (FEBT) Doses (mcg)
200	100
400	100
600	200
800	200
1200	400
1600	400
N/A	600
N/A	800

Adapted from the Fentora[®] package insert.⁵

COST, DOSE, AND HOW SUPPLIED

Fentanyl effervescent buccal tablets are supplied in 100, 200, 400, 600, and 800 mcg strengths. The average wholesale prices (AWP) for the 100 mcg and 200 mcg FEBT are \$13.08 and \$16.56, respectively. The AWP for equivalent doses of the OTFC formulation are \$33.12 for the 400 mcg dose and \$48.08 for the 800 mcg dose, respectively (see Table 2 for dose comparisons).

Fentanyl buccal tablets do not have equal potency to other fentanyl formulations.^{3,5,6} Caution is advised when changing from one fentanyl formulation to another. Specifically, oral transmucosal fentanyl citrate is not equipotent to fentanyl buccal tablets (Table 2).^{5,6} All patients who are naïve to transmucosal fentanyl therapy should initiate FEBT therapy at the 100 mcg dose, regardless of the type or magnitude of their long- and short-acting opioid doses. Patients may repeat the same dose of FEBT one time 30 minutes after the initiation of the first dose if symptoms have not resolved.⁵ Response to therapy should be reassessed within days to determine if the current FEBT dose is sufficient. Dose titration should occur if the starting dose is insufficient to control BTP.

The blister pack containing each dose should not be opened until immediately prior to administration and the tablet should not be split or broken. Fentanyl buccal tablets should be placed between the cheek and gum above a molar, allowed to dissolve for 30 minutes, and any remaining tablet swallowed with a full glass of water. The FEBT formulation generally takes between 14 and 25 minutes to dissolve. Fentanyl buccal tablets will have significantly reduced efficacy if swallowed whole or without 30 minutes of continuous buccal contact.

CONCLUSION

Fentanyl effervescent buccal tablets have demonstrated a statistically significant improvement over placebo in pain rating scales for the treatment of BTP in patients with chronic cancer pain and low back pain. The clinical significance of these findings is not clear. According to current literature, the difference in pain intensity shown in these studies does not represent a meaningful clinical improvement.¹¹ While FEBT has clearly been shown to have a favorable pharmacokinetic profile over OTFC and other short-acting oral opioid therapies, there have been no published trials comparing FEBT to the same alternatives for differences in pain rating scales for BTP.

Given the lack of studies comparing the FEBT formulation

to other oral opioid therapy, and the improved pharmacokinetic profile over the lollipop formulation, it is useful to evaluate studies that compare the lollipop formulation to standard oral opioid therapy. In a double-blind, double-dummy, randomized, multiple crossover, multi-center study the lollipop formulation was compared to immediate-release morphine sulfate (MSIR) for the treatment of breakthrough cancer pain.¹⁴ The primary outcome measure, PID at 15 minutes, statistically favored OTFC over MSIR. All secondary measures (PID, PR, and GMP) were statistically significantly improved for OTFC over MSIR at all time points. While the average difference in PI scores between OTFC and MSIR are only reported graphically in this study, they clearly differ by less than 1 point on the 11-point scale at any measurement time. This again calls into question the clinical significance of the pain intensity improvement.

Fentanyl effervescent tablet and transmucosal lollipop formulations have small statistically significant benefits over placebo and conventional short-acting opioid therapies for breakthrough pain. The FEBT formulation could replace the OTFC formulation in therapy due to decreased cost and improved pharmacokinetic profile. Both of these therapies, however, come with a much higher price tag than oral short-acting opioids and often require prior authorization through prescription benefit plans. Given the current lack of data to support clinically significant superiority, the fentanyl effervescent buccal formulation should be reserved for second- or third-line use after a trial of oral short-acting opioid therapy has not provided adequate breakthrough cancer pain relief. ●

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REFERENCES

1. Fine PG. Breakthrough Cancer Pain: Epidemiology, Characteristics and Management. *CNS Drugs* 2000; 13:313-319.
2. Bennett D, Burton A, Fishman S, Fortner B. Consensus panel recommendations for the assessment and management of breakthrough pain. Part 2 Management. *P&T* 2005; 30:354-361.
3. Blick S, Wagstaff AJ. Fentanyl buccal tablet: in breakthrough pain in opioid-tolerant patients with cancer. *Drugs* 2006; 66:2387-93.
4. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain, version 1, 2006 http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf.
5. Fentora [Package Insert]: Frazer, PA: Cephalon, Inc; 2006.
6. Darwish M, Tempero K, Kirby M, Thompson J. Relative bioavailability of the fentanyl effervescent buccal tablet (FEBT) 1080 pg versus oral transmucosal fentanyl citrate 1600 pg and dose proportionality of FEBT 270 to 1300 pg: a single-dose, randomized, open-label, three-period study in healthy adult volunteers. *Clin Ther* 2006; 28:715-724.
7. Darwish M, Tempero K, Kirby M, Thompson J. Pharmacokinetics and dose proportionality of fentanyl effervescent buccal tablets in healthy volunteers. *Clin Pharmacokinet* 2005; 44:1279-86.
8. Micromedex® Healthcare Series [Internet database]; Greenwood Village, Colo: Thomson Micromedex.
9. Farrar JT, Young Jr JB, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94:149-158.
10. van der Roer N, Ostelo RW, Bekkering GE, et al. Minimal clinically important change for pain intensity, functional status, and general health status in patients with nonspecific low back pain. *Spine* 2006; 31:578-582.
11. Ostelo R, de Vet HCW. Clinically important outcomes in low back pain. *Best Pract Res Clin Rheumatol* 2005; 19:593-607.
12. 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; 22:805-811.
13. Portenoy RK, Messina J, Xie F, Peppin J. Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. *Curr Med Res Opin* 2007; 23:223-233.
14. 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; 91:123-130.
15. Olkkola KT, Palkama VJ, Neuvonen PJ. Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. *Anesthesiology* 1999; 91:681-685.
16. Bowdle TA. Adverse effects of opioid agonists and agonist-antagonists in anaesthesia. *Drug Saf* 1998; 19:173-189.
17. Darwish M, Kirby M, Robertson PJ, et al. Single-dose and steady-state pharmacokinetics of fentanyl buccal tablet in healthy volunteers. *J Clin Pharmacol* 2007; 47:56-63.
18. Actiq [Package Insert]: Frazer, PA: Cephalon, Inc; 1998.

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