CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

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Division of Anesthetic, Critical Care, and Addictive Drug Products Clinical Review of NDA

NDA #	20-747
Sponsor:	Anesta
Brand Name:	Actiq
Drug Category:	Opioid Analgesic
NDA Classification:	6B
Indication:	Relief of Breakthrough Pain in Opioid-Tolerant Cancer Patients with Chronic Pain.
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1.0 Background

Fentanyl, a highly lipophilic synthetic phenylpiperidine derivative, has extensive clinical use in anesthesia and critical care as a primary intravenous analgesic agent and the principle component of Total Intravenous Anesthesia. Because of its high lipid solubility, intravenous fentanyl has a high potency, approximately 70-100 times that of intravenous morphine sulfate, and achieves a blood-to-brain concentration of unity in one circulation time. Its major metabolite, nor-fentanyl, is inactive in the circulation. In clinical use by anesthesiologists for more than 25 years as the intravenous opioid analgesic of choice for general anesthesia, sedation/analgesia, and continuous sedation of mechanically ventilated critically ill patients, fentanyl has an established safety record. Because of its potency as a mu-receptor agonist, the expected side effects of somnolence and hypoventilation are continuously monitored when fentanyl is administered intravenously.

Oral transmucosal fentanyl (OTFC) is a solid formulation of fentanyl citrate incorporated into a sweetened soluble matrix on a handle, intended for oral administration by sucking. The development of fentanyl citrate as an oral lozenge takes advantage of its rapid and clinically significant bioavailability when absorbed by the transmucosal route. By this route, fentanyl has a bioavailability of approximately 50%, representing a combination of rapid absorption across the oral mucosa and slower absorption through swallowing and transport across the gastrointestinal mucosa.

The sponsor is currently marketing this product as Fentanyl Oralet 100, 200, 300 and 400 μg (NDA 20-195) for use as a pre-anesthetic sedative and as an analgesic/sedative for painful invasive procedures. At the time of approval of Fentanyl Oralet, it was the intention of the sponsor to conduct further studies to support an indication in chronic treatment of patients with cancer pain. It is this indication which is the subject of the current NDA.

Administrative History

2.0 Materials Reviewed

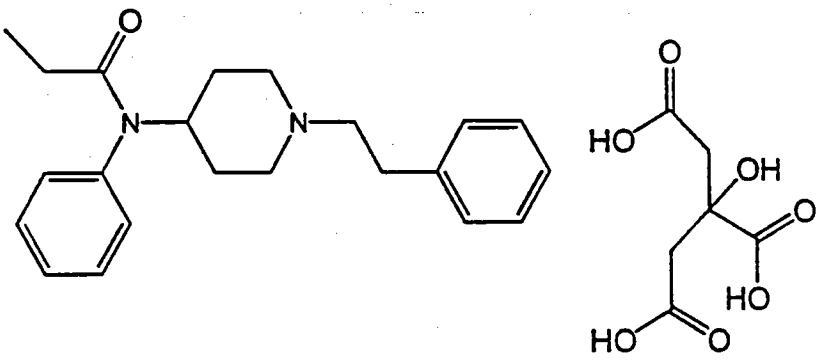
Review documents for efficacy included the original Final Study Reports from the Clinical Development Program, the sponsor's Integrated Report of Efficacy submitted in support of the NDA, and the completed primary reviews. Review documents for safety included the original Final Study Reports, the sponsor's Integrated Safety Report submitted in support of the NDA, the completed primary reviews, and the first Safety Update Report, dated April 14, 1997.

One additional study, AC200/015 was also reviewed and the efficacy, safety and pharmacokinetic data that was obtained will be included in this report. Although the study was not conducted to specifically support this NDA, subjects from this study were later recruited to participate in the long-term safety study that was conducted in support of the NDA.

3.0 Chemistry

Fentanyl is a 4-phenylpiperidine derivative, molacular weight = 528.6. It is an almost white, colorless powder with a bitter taste. Aqueous solubility is 1g/40 ml. The free base has a pKa= 8.4. Octanol/water partition coefficient is 860/1, indicating high lipid solubility and correlating with analgesic potency. Fentanyl should be stored in a closed container and protected from light.

Chemical formula:



Fentanyl citrate lozenges, marketed as Actiq, contain 200, 400, 600, 800, or 1600μg/unit- each unit weighs 2.38 g. The candy matrix contains white color (titanium dioxide), raspberry flavor, corn syrup solids and sucrose. Drug-to-exipient ratios are not constant for all strengths. The candy matrix is attached to a white stick with a screw end. Packaging is in a foil pouch of composed of PET, Valeron, foil, polyethylene. The foil pouch is consumer tested for child resistance, and requires scissors to open.

4.0 Animal Pharmacology/ Human Pharmacology

Because fentanyl citrate has been marketed for more than twenty years as a

parenteral agent, the animal pharmacology, toxicology, mutagenicity, and teratogenicity of fentanyl are already described. Therefore, new animal pharmacology studies were not performed for this NDA.

Human pharmacokinetic studies were performed to establish a dose-response relationship between oral transmucosal administration of the different strengths of Actiq lozenges and bioavailability of the various strengths. A complete review of the pharmacokinetics of Actiq is presented in the Clinical Pharmacology and Biopharmaceutics Review, with salient points summarized here.

Complete ingestion by sucking in 15 minutes achieves the best bioavailability of Actiq. Ingestion in more or in less time results in less efficiency of absorption of the product. This is because fentanyl absorbed directly across the buccal mucosa achieves direct bioavailability into the blood stream, while fentanyl which dissolves in saliva and is swallowed achieves delayed absorption across the gastric mucosa, and undergoes first pass metabolism through the enterohepatic circulation. Because of delayed absorption from the gastrointestinal tract, if a significant portion of the lozenge is chewed or swallowed, both lower peak blood levels and delayed elimination result. Overall, with correct sucking technique, the fentanyl in Actiq has a bioavailability of approximately 50%. The mean peak plasma concentration of fentanyl after 15 μg/kg OTFC is 2.7 NG/ml (range 1.4-4.6 NG/ml).

The sponsor tested the potential for accumulation with repeat dosing in normal adults, using an 800 μg unit administered every 6 hours, and did not demonstrate accumulation or prolongation of the elimination phase (AC200/005). In the clinical studies conducted with cancer patients, each Actiq unit dose could be repeated every fifteen minutes for four doses if pain relief was inadequate, and episodes of breakthrough pain could be treated as often as every four hours. Thus, study AC200/005 did not offer sufficient information on the potential for accumulation, based on the recommended protocol. AC200/015, attempted to address this question in the target population. Adult cancer patients (n = 20) substituted Actiq for their around-the-clock analgesic, using the dose determined to be effective for control of pain with a single unit. In this study, all doses except 1600 μg were used, and intervals varied from four to eight hours, based on patient requirement. Dose normalized ratios of Cmax (final:initial) were close to unity, indicating that accumulation of drug had not occurred. However, there were isolated patients with high final blood concentrations, suggesting that cumulative pharmacokinetics are not entirely predictable. Another shortcoming is that no data was obtained for the 1600 μg dose, since no patient in the study arrived at this dose for effective pain control.

The peak plasma concentrations of fentanyl obtained after each unit dose is summarized in the Table 1 below, which combines the data from studies AC200/009 and AC200/015.

Table 1. Peak Blood Concentrations of Fentanyl after Oral Transmucosal Fentanyl Citrate; Summary of Data from Two Pharmacokinetic Studies.

OTFC Dose (μg)	C_{max}, mean + SD (ng/ml)	
	AC200/015	AC200/009
200	0.39 ± 0.28	0.39 ± 0.09
400	0.77 ± 0.22	0.75 ± 0.25
600	1.27 ± 1.42	
800	1.26 ± 0.40	1.55 ± 0.47
1200	2.58 ± 1.15	
1600		2.51 ± 0.57

5.0 Proposed Indication, Dosage Form and Strength, Route of Administration, and Directions for Use

The proposed indication for use of Actiq is the palliative treatment of breakthrough pain associated with chronic pain of advanced cancer, in patients who already require continuous opioid therapy for pain control and are tolerant to the side effects of opioid agents.

Typically, pain control for these patients is achieved by titration of a long-acting opioid agent, such as extended-release morphine or transdermal fentanyl, the endpoint being relief from constant pain. Despite this therapy, however, patients experience "breakthrough episodes" which may be brought on or exacerbated by movement, coughing, Valsalva, etc., or may be unrelated to activity, as from pain caused by tumor invasion of nervous structures or visceral organs. The "around-the-clock" medication is adjusted to alleviate most pain and minimize the number of intense breakthrough episodes, while a second short-acting agent is added to treat these episodes as needed. The type and dose of both the long-acting and short-acting agents chosen to treat pain is based on the individual patient's experience in obtaining relief and tolerance of adverse effects.

For the treatment of an episode of breakthrough pain with Actiq, the patient is instructed to suck on a single unit of Actiq, moving it around in the mouth so as to maximize exposure of the drug to the oral mucosal surface area, and to completely dissolve the unit within fifteen minutes. As indicated earlier, chewing or swallowing the drug reduces its effectiveness, as a larger proportion of fentanyl would then be subject both to delayed absorption across the gastric mucosa, due to ion trapping, and then to first-pass metabolism through the enterohepatic circulation.

A range of doses/ unit were tested clinically by the sponsor, with the intention of marketing Actiq in all tested dose strengths: 200 μg, 400 μg, 600 μg, 800 μg, 1200 μg, and 1600 μg. The intention of the sponsor is to make a range of doses available such that each patient, through a process of titration, could find the single unit strength that would be effective for controlling the majority of breakthrough episodes, with tolerable or minimal side effects, and to minimize the

incidence of partially used units being saved out of their packaging for possible re-use.

6.0 Description of Clinical Data Source

Seven clinical trials were conducted for this NDA, consisting of three randomized studies of OTFC in the immediate postoperative period, three randomized studies in chronic pain patients, and one open-label safety trial of chronic patients who had been recruited from prior studies. An additional pharmacokinetic study in cancer patients,* already referred to in Section 4.0, was performed to provide additional data on peak and final blood concentrations under conditions of clinical use, and was a recruitment source for subjects in the long-term safety trial.

Studies in postoperative patients:
AC 200/P10: A pilot trial designed to estimate the minimally effective dose of OTFC to be used in AC 200/010.
AC 200/010: A double-blind trial of OTFC vs. intravenous morphine to establish relative potency, using a "four point assay" design, that is, a low dose and a high dose of each agent.
AC 200/006: Multiple-dose double-blind placebo-control trial of OTFC q 3 hrs x 4 doses, comparing morphine sparing effect in patients receiving morphine patient controlled analgesia (PCA).

Studies in chronic cancer patients:
AC200/011: Dose titration of OTFC for episodes of breakthrough pain against background use of oral morphine.
AC200/012: Dose titration of OTFC for episodes of breakthrough pain against background use of transdermal fentanyl.
AC200/013: Dose titration study of OTFC for episodes of breakthrough pain against a background of long-acting opioid use, followed by a double-blind placebo-controlled crossover phase.
AC200/014: Open-label, long-term use of OTFC for breakthrough pain in patients enrolled from previous studies; study was ongoing at the time of the filing of the NDA.
AC200/ 015*: Open-label, crossover study of the pharmacokinetics, efficacy and safety of OTFC for persistent pain, when substituted for approved around-the-clock opioid regimens. Summary data from this study are added in italics to Table 2.

* AC200/015 was not part of the clinical development program of the NDA, since the sponsor does not seek an indication for Actiq as an around the clock therapy for intractable pain.

Table 2: Summary Information of Design of Clinical Studies Performed Under IND in Support of this NDA (extracted from Sponsor's Table 1-1, ISS)

Study	Population	Treatment	# of Subjects	Duration
AC200/P10	postoperative adults: lower abdominal surgery	OTFC 200 μg, 400 μg	10 11	1 administration
AC200/006	postoperative adults: total hip or knee arthroplasty	PCA + placebo, or 400 μg, or 800 μg	37 40 37	q3 hrs x 4 administrations
AC200/010	postoperative adults: lower abdominal surgery	OTFC 200 μg, or OTFC 800 μg, or MS 2 mg iv, or MS 8 mg iv	33 32 34 34	1 administration
AC200/011	adult cancer patients	OTFC 200-1600 μg/ unit dose	65	2 - 20 days
AC200/012	adult cancer patients	OTFC 200-1600 μg/ unit dose	62	2 - 20 days
AC200/013	adult cancer patients	OTFC 200-1600 μg/ unit dose, or placebo	130	4 - 44 days
AC200/015	*adult cancer patients*	*OTFC 200-1600 μg/ unit, crossover to approved long-acting opioid*	*20*	*3 - 12 days*
AC200/014	adult cancer patients	OTFC 200-1600 μg/ unit dose	94*	4 month blocks

*155 as of filing of updated safety report, 4/16/97

Additional studies originally submitted as part of NDA 20-195 (Fentanyl Oralet) were submitted in synopsis form in support of efficacy of OTFC for the relief of pain:

AC200/001: Open compassionate use of OTFC for the treatment of breakthrough pain in a single patient with chronic cancer pain. Initial evaluation during the study period of vital signs and oxygen saturation (SpO2) showed no change compared to baseline during administration of one 700 μg unit of OTFC per day. In the subsequent 80 day study period the patient used up to five (1000 μg/unit) doses/day, and reported onset of pain relief within 2-5 minutes, peak relief

at 20 minutes, with no adverse effects.

AC200/002: Five patients were enrolled for an open pilot study of self-administration of OTFC or Oral Morphine Sulfate (MS) 25-75 mg every three hours for breakthrough pain. Patients were scheduled randomly to take OTFC or MS for two week alternating blocks for a total of six weeks. Pain scores and onset of analgesia were recorded 4 times/day at baseline and for the treatment period. Three patients completed all segments; 1 patient withdrew for placement of an epidural catheter, and 1 patient withdrew from the MS segment due to nausea and vomiting. Both drugs were effective: 283/285 episodes for OTFC, 99/102 episodes for MS. Onset of analgesia was faster for OTFC compared to MS in the first 10 min (45.3% vs. 7.8%, respectively). Adverse events for OTFC were one report each of dizziness, nausea and vomiting, and urinary retention.

AC200/003: Ten hospitalized patients were enrolled for the determination of efficacy and safety of OTFC 10-15 μg/kg self-administered up to six times/day over 12 hours (7 am-7 pm) for two days, as needed for breakthrough pain. Eight patients used OTFC four times and two patients used OTFC five times. The median dosing interval was 4 hours and 37 minutes. OTFC was associated with: 1) pain relief with median onset time of 9.5 minutes, 2) increased sedation observed at 10-30 minutes after use, 3) no clinically significant changed in vital signs or SpO2 during two hours of monitoring. Adverse events included episodes of desaturation, blurred vision, bad taste, nausea, numbness, and pruritis.

AC200/004: Patients previously enrolled in AC200/002 were given the opportunity to continue open-label use of OTFC. Two patients elected to participate, and continued to use OTFC for 10 months. Data was not reported consistently; however, OTFC was assessed by the participants to be effective for relief of breakthrough pain, and no adverse events were reported.

AC500/009: An open label randomized clinical trial of 30 postoperative adult patients was conducted to test efficacy and safety of 400 μg (4.09-7.09 μg/kg) and 800 μg (7.77-12.9 μg/kg) unit doses of OTFC. Both doses produced sedation in >50% of each dose group and analgesia in 77% of patients at the 400 μg dose, and 82% at the 800 μg dose. These effects became manifest approximately 20-30 minutes after the dose. Over the same time period, mean SpO2 was noted to fall from 96% to 95%. Adverse events were nausea, vomiting, hypertension, and hypoxemia (as measured by pulse oximetry) in a total of 6 patients, three from each dose group. Three patients from both dosage groups (400 μg: 2, and 800μg: 1) required verbal stimulation in order to maintain SpO2 > 89%.

The data from the studies conducted under NDA 20-195 provided essentially proof-of-principle experience, identifying whether the available dose strengths of Fentanyl Oralet could treat acute painful episodes in both postoperative patients and chronic cancer patients. The data from these trials was not incorporated by the sponsor into the efficacy or safety database of NDA 20-747. In reviewing these studies, no unusual findings were encountered and they are consistent with the

data of the clinical development program discussed below.

6.1 Primary Development Program

6.1.1 Study Type and Design/Patient Enumeration

Acute Pain Studies:

The studies in acute postoperative patients were performed to demonstrate the analgesic efficacy of OTFC, and to calculate a morphine: OTFC potency ratio. Efficacy was measured by two parameters in these studies: 1) VAS scores for quantitation of subjective pain, and 2) morphine-sparing effect, as patients were allowed to episodically self-administer morphine intravenously (patient-controlled analgesia, PCA) as required for pain. Across these studies, OTFC was consistently demonstrated to achieve analgesia by both criteria. In this opiate-naive population the overall incidence of clinically significant episodes of respiratory depression was 39.6%. Patients were: 18-79 years old, male or non-pregnant female, ASA I-III, 40-100 kg, with no history of opioid medications.

21 patients were randomized to receive OTFC in one of two doses to identify whether the 200 or 400 μg dose would exert a significant morphine sparing effect after lower abdominal surgery. To meet patients' initial postoperative analgesic requirements, the patients received intravenous morphine PCA for the first 12 hours postoperatively. After the first 12 hours, the PCA morphine infused was recorded as the "baseline" rate of administration. At the first subsequent request for analgesia, a randomized, blinded, single dose of OTFC was given, and the patients were followed until the next request for analgesia, or for 6 hours. By pain intensity scores, it was found that both 200 μg and 400 μg dosage units provided meaningful pain relief, for 9/10 patients and 8/11 patients in these respective dose groups. There was 1 patient who withdrew because of inadequate pain relief within 5 minutes of receiving OTFC. There were no incidents of respiratory depression in this study.

In a randomized double-blind, parallel-group study conducted at two centers, two doses of OTFC were compared to each other and placebo. Post-operative orthopedic patients in the PACU, upon requesting pain relief, received morphine PCA after completing a dose of: placebo, 400, or 800 μg OTFC. Four doses of OTFC at three hour intervals were evaluated. 114 patients received at least one administration of the study drug. There were 55 protocol violations in 35 patients. Evaluability for efficacy was determined after study completion and before the blind was broken. Subjects were considered evaluable if there were three hours of data available for the administration period. For the first administration of OTFC/placebo, there were 101 fully or partially evaluable patients, for the second administration there were 92 patients, for the third administration there were 77 patients, and for

the fourth administration there were 75 evaluable patients. Withdrawals are summarized in Table 3.

Table 3. Summary of Completion Status of Acute Postoperative Patients in a Placebo-Controlled Trial (AC200/006).

	400 μg	800 μg	Placebo
Completed	31	26	30
Adverse Event	9	10	6
Other	0	1	1
Total	40	37	37

A third study conducted in postoperative patients to determine the OTFC: iv morphine relative potency utilized a randomized, double-blind, parallel group design of 133 patients after lower abdominal surgery. Patients received either an active dose of OTFC, 200 or 800 μg, + a placebo intravenous morphine injection, or active intravenous morphine, 2 or 8 mg, + placebo OTFC. Among the parameters measured were onset of analgesia, VAS scores, and global pain relief. Patients were randomized as follows: OTFC 200: 34, OTFC 800: 33, morphine 2: 34, morphine 8: 34. 2 patients did not receive drug (OTFC 200: 1, OTFC 800: 1). 10 patients were unevaluable for efficacy and were evenly distributed among the four groups.

In summary, in the acute pain studies a total of 143 healthy postoperative patients, with no prior history of drug tolerance, received OTFC as a analgesic, either alone or concomitantly with intravenous morphine PCA. These studies demonstrated that OTFC had a significant analgesic effect, as demonstrated by reduction of intravenous morphine on demand, with onset of action in approximately 5-10 minutes from administration of the dose. A four-point comparison of pain relief variables identified the OTFC: iv morphine potency ratio in the range of 7.9 - 14.

Studies in Chronic Cancer Patients:

The cancer population studied in this series are the target population of intended prescription of Actiq. These patients use daily long-duration opioid therapy for chronic pain, for example, extended-duration oral morphine, or transdermal fentanyl, plus a second opioid medication to treat breakthrough pain episodes. Patients receiving opioids by other routes of administration, specifically intrathecal

or epidural, were excluded from these trials.

Studies AC200/011 and 012 were short-term dose titration studies designed to establish the clinical setting and method of use of OTFC as a therapy for episodes of breakthough pain. Study AC200/013 was an efficacy trial in which an initial phase of individual titration to the effective dose was followed by a placebo-controlled phase. Study AC200/014 was an open-label, long-term safety study which recruited patients who had already had acceptable clinical responses to OTFC in the above titration studies; therefore, efficacy was not a primary endpoint in the latter study. OTFC was substituted for the patient's usual breakthrough medication for up to four episodes of breakthrough pain per day.

Because the dose-titration trials were identical in design except for the background of long-acting opioid analgesic, they are presented in aggregate here. 127 patients enrolled in the dose titration studies, ages ranged between 18-79 years. Disposition of patients is described in Table 4.

Table 4. Combined Population Disposition for Two Dose Titration Studies in Cancer Pain Population (AC200/011, 012)

Patients entered	Withdrawals	Reasons for withdrawals:			
		related to disease	uncontrolled pain	AE: related	other
65	17	5	5	3	4
62	15	3	4	3	5
Totals: 127	32	8	9	6	9

During the baseline phase, patients evaluated their breakthrough pain and the performance of their regular rescue pain medicine for two days. During the titration phase, OTFC was substituted for the treatment of up to two breakthrough pain episodes per day. Up to four OTFC units separated by at least 15 minutes could be used for each episode requiring treatment. Patients also had the option of using their regular rescue medication after 30 minutes of inadequate pain relief. The requirement for more than one unit was the basis for escalating to the next higher dose, while experience of adverse effects was the criterion for reducing the dose. Patients had up to 20 days to achieve successful completion of two consecutive days of OTFC at a single unit dose per episode. Patients maintained a daily diary, evaluating their pain intensity, pain relief, and global performance of OTFC, as per baseline conditions. In a blinded fashion, as a method of identifying a clinical dose-response relationship, one third of orders to increase the dose were ignored, i.e., the patient received the same dose as for the previous breakthrough episode, despite a prior inadequate response.

Study AC200/013 entered 130 patients with 92 completions. There were 8

withdrawals due to serious adverse events: 2/8 were judged to be possibly related to study medication; 14 withdrawals due to other adverse events, judged to be possibly related to study medication, and 16 withdrawals for non-adverse event reasons. The study was designed as a randomized double-blind trial, in which titration to the effective dose of OTFC for episodes of breakthrough pain was followed by a blinded placebo-controlled phase. After identification of the individual effective dose, the patient was issued, in a blinded fashion, 10 OTFC units, seven at the effective dose and three placebos, and instructed to use one unit per episode sequentially, with rating of pain intensity, pain relief, and global evaluation as in previous efficacy studies. The duration of participation in this trial ranged from 4 to 44 days. In the dose-titration trials, a strict stepwise increase in dose was ordered by the investigator through the available dosage strengths. Since patients could use up to four units at a given strength per episode (every 15 minutes for one hour), there was some variability in the total dose used to treat each episode, both within and between titration steps. Nevertheless, the majority of patients were successful in identifying a single unit dose that was satisfactory for treatment of a single episode using this methodology. In the placebo-controlled trial, the titration scheme was designed to give the individual patient greater discretion in determining the effective dose, in that the patients were given a range of dose units from which to choose, and instructed to "start low." Thus, patients were more independently responsible for determining their effective dose during the titration phase, and as a result, variability in the dose for each episode was also observed. As in the dose-titration trials, however, the patients who went on to the second phase of the trial (comparison to placebo) were able to identify an effective dose such that one unit could be used to successfully treat a breakthrough episode, even in individual cases where they had used a higher dose in the titration phase.

Study AC200/014 was an open-label, long-term safety study in which chronic cancer patients who had participated in the dose-titration, placebo controlled, and bioavailability trials (AC200/015) continued to use OTFC at their identified effective dose for treatment of breakthrough pain episodes. Patients participated for four month blocks, continuing to use one unit dose of OTFC per episode of breakthrough pain, and maintaining diary recording of breakthrough pain episodes, pain relief, and adverse events. Titration to a higher or lower dose was possible during the course of participation and follow-up with the investigator. As of the safety update of November, 1996, there were 151 patients treated for a total of 13,742 days for 38,595 episodes of breakthrough pain.

6.1.2 Demographics

Demographics of the dose-titration studies and the placebo-controlled study in chronic cancer pain patients are summarized in Table 5. The patient characteristics are similar. Because patients participating in the safety study were

recruited from the dose titration studies, their demographics are identical to those represented in the table below.

Table 5. Demographics of Participants in Dose Titration Studies

	Age: mean range	Gender: male female	Weight: mean range	Race: White/ Black/Hispanic/Asian
AC 200/011	53 (yr) 26-74	28(43%) 7(57%)	70 (kg) 27-137	53(82%)/5(11%)/7(8%)/--
AC200/012	59 (yr) 25-91	29(47%) 33(53%)	67 (kg) 39-101	57(92%)/--/3(5%)/2 (3%)
AC200/013	54 (yr) 27-84	41(45%) 51(55%)	70 (kg) 40-129	86(93%)*/5(5%)/--/1(1%) *identified as "other"

In the dose titration studies, 80% of patients identified their target breakthrough pain as nociceptive, and 19% identified their breakthrough pain as neuropathic. In the long-term safety study, the distributions were 78% and 21% respectively. There was no relationship subsequently demonstrated between the type of pain and the efficacy of Actiq.

6.1.3 Extent of Exposure (Dose/Duration)

The entire study program was conducted in the United States. No reference is made to drug experience in other countries under the IND or otherwise. Table 1 above identifies the duration of exposure of the patient population in each study. As each patient used more than one unit per day, the aggregate exposure for chronic pain patients represents multiple daily uses of Actiq. As of November 15, 1996, 151 patients participating in the long-term safety study used 41,766 units to treat 38,595 episodes of pain for a total of 13,742 days. The sponsor's table of investigators is reproduced in the Appendix to this report.

6.2 Secondary Sources

None.

6.2.1 Non-IND Sources

None.

6.2.2 Post-Marketing Experiences/ Literature

The medical literature has provided a limited secondary source of drug experience with the fentanyl lozenge, since it has been marketed since 1994 as Fentanyl Oralet for the indication of preoperative sedation and analgesia. Efficacy and safety data from these sources are consistent with the known mu-receptor opioid-agonist effects of fentanyl by all routes of administration. Because the indication for Fentanyl Oralet is sedation, this effect is not considered an adverse effect in the context of preoperative or pre-procedural use. No off-label uses for Fentanyl Oralet have been reported other than the studies conducted under this NDA.

7.0 Summary of Human Pharmacokinetics

Human pharmacokinetics, as discussed above, indicate transmucosal administration of fentanyl citrate occupies an intermediate position between intravenous administration and a swallowed oral solution. (See Appendix). The pharmacokinetics of transdermal fentanyl, which delivers 50-150 μg/hr, is different from other routes of administration because of the delay in achieving an effective blood concentration until 8-12 hours after application, and prolonged elimination phase over greater than 24 hours after removal of the transdermal fentanyl patch. All routes of administration achieve efficacy at a minimal blood concentration of approximately 1.0 ng/ml or greater, and respiratory depression is a potential effect at blood concentrations or ng/ml. However, the relationship between respiratory depression and blood fentanyl concentration has been characterized for opioid non-tolerant individuals only. Tolerance to the respiratory depressant effects of opioid agents has been identified for chronic use of morphine and methadone. After acute administration of fentanyl, recovery from the respiratory depressant effects closely parallels the decline of plasma levels. Other serious adverse effects of fentanyl, i.e., chest wall rigidity and myoclonus, are assumed to be associated with high doses delivered rapidly, but this relationship has not been fully characterized. Chest wall rigidity has been reported only in patients undergoing general anesthesia, and may be provoked by the co-administration of nitrous oxide. The following figure reproduces the delivery characteristics of intravenous, transmucosal and gastric administration of fentanyl citrate.

Because age differences in the pharmacokinetics of fentanyl are well described, no specific studies were done to identify these differences. Adults older than 60 years of age are known to experience higher blood concentrations of fentanyl and other opioids administered on a weight basis. Data from the clinical trials, comparing mean effective dose of Actiq according to age, are presented.

8.0 Efficacy Findings

Dose titration studies:

AC200/011: 65 patients using long-acting morphine around-the-clock and an immediate release opioid medication for breakthrough pain entered this study. Of 65 patients entering this study, 48 patients were able to find a successful dose of OTFC by titration by day 20 of the titration phase. Global performance of OTFC was rated at 2.74, vs 2.08 for regular rescue ($p = 0.0002$). For these patients comparisons of pain relief for OTFC were better than regular rescue medication at 15 minutes after onset of treatment (pain intensity difference 2.91 vs 1.31, $p = 0.0001$). At subsequent time points (15 minute intervals to 60 minutes), the differences were not significant. Comparisons for pain relief were also significantly better at 15 minutes (2.91 vs 1.31, $p = 0.0001$), not significantly different at 30 minutes, and again reached significance at 60 minutes (5.15 vs 4.07, $p = 0.02$). However, the timeline of titration of OTFC was potentially 20 days for these subjects, making the baseline comparison to the regular rescue medication a historic, rather than a head-to-head comparison.

10/32 patients randomized to start at 200μg and 12/33 randomized to start at 400μg achieved successful pain relief at the starting dose. For the entire group started at 200μg, the effective dose was 640 $\pm$ 374μg (mean$\pm$SD), compared to 584 $\pm$ 202μg for the group started at 400μg (two-way ANOVA p value=0.13). The 90% confidence interval for the ratio of the 200 and 400μg doses was 89% to 133%. The sponsor stated "this [confidence intervals between 60% and 140%] indicates that the final dose was equivalent for the two starting groups."

A linear regression was performed between the final OTFC dose and around-the-clock narcotic. No relationship could be demonstrated, suggesting that the decision for starting OTFC for treatment of breakthrough pain requires titration on a case-by-case basis.

AC200/012: 62 patients using transdermal fentanyl for around-the-clock pain control and a short onset opioid for breakthrough pain entered this study. Patients were randomized to a starting dose of either 200 μg or 400 μg of OTFC. However, as a safety precaution, patients whose transdermal fentanyl dose was sufficiently low such that the randomly assigned starting dose of OTFC would be greater than 20% of the total 24 hours transdermal fentanyl dose, the patient was non-randomly assigned to a starting dose of 200 μg. The unblinded assignees were excluded from statistical analysis. 47 patients achieved successful titration of OTFC for breakthrough pain: 13/18 patients randomized to start at 200μg, 8/11 patients randomized to start at 400μg, and 26/33 patients who were not randomized and were all started at 200μg/dose. As in AC200/011, patients had up to 20 days to identify their effective treatment dose of OTFC.

There were no differences in baseline pain severity scores between randomized treatment groups, but the mean age of patients randomized to 200μg was 54 $\pm$ 12 years, compared to 62 $\pm$ 16 years for patients randomized to

400μg; this difference was significant. There were no other significant differences between demographic variables. When regular rescue medications were converted to morphine-equivalent, patients randomized to the 400μg starting dose had a significantly higher rescue dose, 39 ± 29 mg morphine-equivalent (mean ± SD), compared to patients randomized to 200μg, 20 ± 17 mg morphine-equivalent.

For the group randomized to 200μg, the mean effective dose was 677 ± 466μg (mean±SD), compared to 825 ± 345μg for the group started at 400μg. The mean effective dose for the non-randomized treatment group was 469 ± 178μg. The 90% confidence interval for the ratio of the 200 and 400μg doses was 50% to 109%. This confidence interval does not support equivalency for the mean final doses in the two randomized groups, according to the standard range historically used by the agency. Comparing randomized patients only, the difference between the mean effective doses were not statistically significant by two-way ANOVA with factors for starting dose, for center, and for treatment-by-center interactions. As in the previous study of similar design, no relationship between around-the-clock opioid dose and effective dose of OTFC could be identified statistically.

Mean pain relief scores were reported as 4.34 for OTFC, vs 3.32 for baseline medication. Pain relief scores by 15 minute evaluation intervals are summarized in Table 6.

Table 6. Pain Relief Scores (extracted from Sponsor Table 28: AC200/012)

Variable	Number	Rescue at Baseline	OTFC, Successful Days	p value (paired t-test)
PR: at 15 min	40	0.82	1.90	0.0001
15-30 min	39	0.75	0.54	0.13
30-60 min	43	0.74	0.41	0.005
Total PR		2.31	2.85	

The data indicates that the greatest pain relief was achieved at 15 minutes after use of OTFC in comparison to AC200/011, where the analgesic effect of OTFC was identical in onset, but sustained or enhanced over the 60 minute observation period. Mean Global Performance rating for OTFC was 2.68, compared to 2.01 for regular rescue. This difference was not statistically significant by two-way ANOVA, with factors for starting OTFC dose, treatment center, and treatment dose-by-center.

Because of the small sample sizes in the randomized groups, the efficacy conclusions from AC200/012 are limited, but consistent with the evidence of efficacy observed in AC200/011. Because of the time separation between the

evaluation of regular rescue and OTFC, the same considerations apply regarding the these comparisons in this study as in the previous study.

8.1 Adequate and Well-Controlled Trials Pertinent to Efficacy Claims

AC200/013: This was the placebo-controlled efficacy trial in the target population. Patients were eligible to participate who were taking either morphine or transdermal fentanyl for around-the-clock analgesia, and experiencing 1-4 episodes of breakthrough pain/day. After a period of titration, patients who achieved effective pain relief from a single dosage strength of OTFC were eligible to enter the double-blind crossover phase. Patients who were unsuccessful in achieving pain relief for more than one month or at the highest tolerable dose of OTFC were discontinued from the study. Therefore, patients had up to one month to attempt to identify an effective dose of OTFC by titration through the available dosage strengths. In the placebo-controlled phase, patients continued to use one OTFC unit at their self-determined effective dose for each episode of breakthrough pain. The patient received 10 randomized prenumbered units, 7 at the effective dose and 3 placebo units, which were to be used in order. If no pain relief occurred 30 minutes after ingestion, the patient could take his regular rescue medication. Of 92 patients who entered phase 2, 72 (78%) completed the study, that is, treatment of 10 episodes in 14 days.

For each episode of pain, the patient rated the following variables, as in prior studies, before OTFC and at 15 minute intervals after completion of the dose, for one hour:

- Pain intensity: 0 = no pain → 10 = worst possible, q 15 min x 4
- Pain relief: 0 = none → 4 = complete, q 15 min x 4
- Global assessment: 0 = poor → 4 = excellent, at 60 min

The primary efficacy variables were Summed Pain Intensity Difference (SPID) and Total Pain Relief (TOTPAR), which were derived from the measured variables listed above, as follows:

$$PID_i = P_0 - P_i$$
$$SPID_i = SPID_{i-1} + PID_i$$
$$TOTPAR_i = TOTPAR_{i-1} + PR_i$$

Data were averaged within patient for evaluable treated episodes and placebo episodes. An intent-to-treat analysis of the double-blind phase data included all episodes in the double-blind phase with no exclusions and no imputations. There were 804 episodes in the double-blind phase; unevaluable episodes were 22/247 for placebo and 52/557 for treated episodes. The reasons for an episode being considered unevaluable were: failure to completely consume OTFC unit, observation time(s) outside of the allowable interval, change of around-the-clock medication, less than 2 hours between two episodes of breakthrough pain, treatment of pain other than target breakthrough pain, failure to follow protocol in titration phase.

Within patient averages were analyzed by the following methods:

- Pain intensity (PI), Pain intensity difference (PID), SPID, Pain relief (PR), TOTPAR, global performance evaluation: three-way ANOVA with terms for investigator, subject within investigator, active/placebo, and investigator by treatment interaction.
- SPID and TOTPAR at 60 min, global performance, additional rescue medication (arcsin transformed data): three-way ANOVA with terms for completion status, subject within status, active/placebo, status by treatment interaction.
- PI, PR, at each scheduled time: four-way ANOVA with terms for investigator, around-the-clock medication (oral/patch), investigator by oral/patch interaction, subject within oral/patch by investigator, active/placebo treatment, treatment by oral/patch interaction, investigator by treatment interaction.
- Dose level in phase 2: one-way ANOVA.

For a detailed analysis of the statistical methods, please see the Statistician's Review.

Of 130 patients who entered the titration phase 37 (29%) withdrew before the end of the titration phase: 22 due to adverse event, 15 due to other reasons: breakthrough pain ceased or decreased, preference for usual rescue medication, unable or unwilling to complete treatment diaries, no reason given.
One patient successfully completed the titration phase but did not enter the double blind phase. Of the 92 who entered the placebo-controlled phase, 72 completed. The reasons for withdrawal from this phase were: adverse event (7 patients), radiation therapy (1 patient), per protocol or due to study closure (10 patients), request for other therapy (2 patients).

55% of patients (n =51) were titrated to an effective dose between 200 and 800 μg. 31% (n = 29) reached an effective dose between 1000 and 1600 μg. The remaining patients who were successful required higher doses, and one patient received 7200 μg per episode. The median number of titrations was 3 (range 0-15), and the median number of days necessary to reach the effective dose was 7 (range 2-34). There was no difference between the mean doses of patients who completed and patients who withdrew for any reason (p = 0.57). Table 7 presents that data.

Table 7. OTFC Dose in Phase 2, vs Completion Status (Total n = 92)

OTFC Dose	Completed 10 Units; n (%)	Withdrawal for AE; n (%)	Withdrawal, Other; n (%)	Total Number (%)
200 μg	7 (10)	1 (14)	5 (38)	13 (!4)
400	16 (22)	2 (29)	1 (8)	19 (21)
600	12 (17)	0 (0)	2 (15)	14 (15)

800	14 (19)	2 (29)	2 (15)	18 (20)
1200	12 (17)	0 (0)	1 (8)	13 (14)
1600	11 (15)	2 (29)	2 (15)	15 (16)
mean; SD (p = 0.57)	**808; 452**	**829; 571**	**662; 519**	**789; 468**

Linear regression plots of OTFC dose vs. around-the-clock morphine or transdermal fentanyl did not demonstrate a significant relationship (slope p-value = 0.38, r=0.39, OTFC vs. morphine; p = 0.30, r= 0.24, OTFC vs. transderm fentanyl). As previously mentioned, this finding was consistent across the sponsor's clinical studies in which OTFC was used for breakthrough pain. (AC200/011, AC200/012, AC200/013, AC200/014).

Efficacy variables in evaluable patients: PI, PID, SPID, PR, and TOTPAR scores were lower for OTFC compared to placebo at 15 minutes and all subsequent 15 minute intervals to 60 minutes. These differences were significant ($p<0.0001$). (See Table 8). These differences were observed whether the around-the-clock medication was morphine or transdermal fentanyl. Global performance ratings were higher for OTFC than placebo ($p< 0.0001$). 15% of patients using OTFC used additional rescue medication, compared to 34% of patients using placebo ($p<0.0001$). The sponsor notes that 65% of episodes treated with placebo were not treated with additional rescue medication. This may be attributed to 1) placebo effect, and 2) self-limited nature of breakthrough pain, which has a median duration of 30 minutes.

Table 8. Mean Values of all Pain Evaluation Variables for OTFC and Placebo, AC200/013

Variable	OTFC				Placebo			
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
PI	4.25	3.46	2.99	2.68	4.99	4.50	4.10	3.89
PID	1.62	2.41	2.88	3.19	1.02	1.51	1.91	2.13
SPID	1.62	4.03	6.92	10.11	1.02	2.53	4.44	6.56
PR	1.42	1.80	2.00	2.14	0.93	1.11	1.30	1.33
TOTPAR	1.42	3.23	5.23	7.37	0.93	2.04	3.34	4.67

All differences OTFC: placebo, $p < 0.0001$

Global performance rating (n= 84) for OTFC was 1.98, compared to 1.19 for

placebo, p< 0,0001. 15% of patients using OTFC used additional rescue medication, compared to 34% of patients using placebo (p<0.0001). The sponsor notes that 65% of episodes treated with placebo were not treated with additional rescue medication. This may be attributed to 1) clinically significant placebo effect, and 2) self-limited nature of breakthrough pain, which has a median duration of 30 minutes.

An intent-to-treat analysis was performed, using all data for PI and PR, with the assumption that all measurements were made at the scheduled time and "no last observation carried forward" was used. This comparison follows in Table 9.

Table 9. Intent to Treat Analysis: Mean Pain Intensity and Pain Relief Scores

	OTFC					Placebo				
	0 min	15 min	30 min	45 min	60 min	0 min	15 min	30 min	45 min	60 min
PI	5.84	4.18	3.37	2.60	2.26	5.94	4.86	4.34	3.43	3.07
PR		1.45	1.85	2.21	2.37		0.98	1.19	1.64	1.67

All p-values < 0.0004

The intent to treat analysis indicates that the imputation of scores by last observation carried forward did not significantly affect the results.

8.2 Overview of Efficacy Data

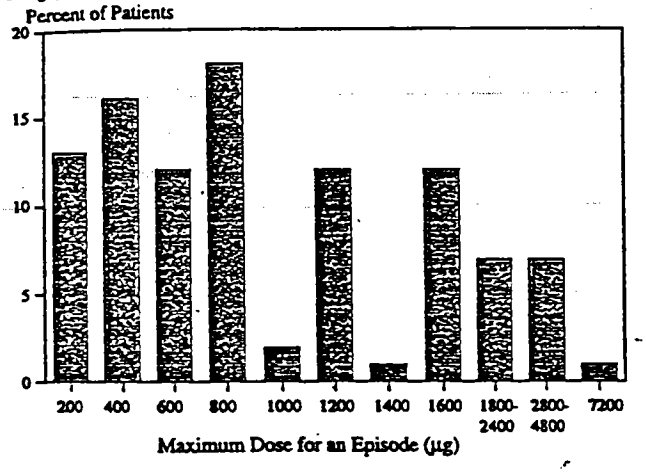
The postoperative trials, presented here in summary only, demonstrated that transmucosal absorption of fentanyl citrate resulted in clinically significant blood levels and analgesia. In this application, a dose of 200 μg of OTFC exerted a degree and duration of pain relief approximately comparable to a single intravenous dose of 2 mg morphine, while 800 μg of OTFC was approximately comparable to the degree and duration of effect of a single intravenous dose of 10 mg of morphine. When administered to postoperative patients also receiving on-demand intravenous morphine PCA, doses of 400 and 800 μg of OTFC reduced demand for morphine by approximately half.

For patients using OTFC to treat breakthrough episodes of pain, the majority of patients (75%) were able to successfully identify a unit dose that was effective. In AC200/011 and 012 combined, there were 9 patients out of 127 entries who failed to achieve adequate analgesia at the highest unit dose strength, 1600μg, including the use of up to four units per episode.

In the placebo-controlled trial, 130 patients were randomized, with 93 who completed the dose titration phase. Of the 92 patients who entered the placebo-controlled phase, 72 achieved successful treatment of breakthrough pain (78%). Three patients in the titration phase and one patient in the placebo-controlled phase

29) reached an effective dose between 1000 and 1600 μg. The sponsor adopted a technique of titration to the effective dose based on commonly used clinical practice with other analgesia agents. While the choice of 200 or 400 μg as a starting dose appeared to make little difference in the dose titration trials, the sponsor's recommendation to start all patients initially at a 200 μg unit dose is preferable for safety reasons for the following reasons: 1) no relationship could be demonstrated between the dose of "around-the-clock" opioid and the effective dose of Actiq in the dose titration trials, 2) higher blood concentrations of fentanyl may be expected in patients older than 60 years of age, and 3) as can be seen in the Sponsor's figure reproduced from AC200/013, 13% of episodes were treated with a maximum total dose of 200 μg, and an additional 16% were effectively treated with 400 μg.

Figure 16. Maximum Total Dose Per Episode in Titration Phase - All Patients Who Received Drug (N=129*)



*One patient's titration phase data were missing

8.3 Other Trials Pertinent to Efficacy Claims

AC200/014 was a multicenter, open-label study of patients taking stable around-the-clock opioid therapy for chronic cancer pain, who also required therapy for episodes of breakthrough pain. 94 patients from previous trials were given a one-month supply of OTFC units in the strength found previously to control episodes of breakthrough pain. Participants visited the clinic monthly, and were contacted weekly by telephone by the investigator. Patients maintained a daily diary in which they recorded the total number of breakthrough episodes, and number of episodes treated successfully and unsuccessfully with OTFC. A "successful treatment" was one in which pain relief was obtained with a single OTFC unit; an "unsuccessful treatment" was one in which additional medication had to be used to treat the episode. Patients continued to take their around-the-clock pain medication. Patients participated for a four-month block of time, and could elect to re-enroll for additional four-month blocks of participation. While this was primarily intended as a safety study, patients who participated continued to keep diary recordings of

treat the episode. Patients continued to take their around-the-clock pain medication. Patients participated for a four-month block of time, and could elect to re-enroll for additional four-month blocks of participation. While this was primarily intended as a safety study, patients who participated continued to keep diary recordings of efficacy variables (e.g., pain relief, global evaluation), which were analyzed descriptively for study purposes, and also used by investigators to determine the need for further titration of the Actiq dose over time.

Global evaluation of performance of OTFC was compared on a monthly basis.

Table 10. Summarized from Sponsor's Table 20, AC200/014

Month 1 (n=90)	Month 2 (n=64)	Month 3 (n=47)	Month 4 (n=37)	Months 5-8 (n=24)	Months 9-12 (n= 10)	Months > 12 (n=4)
3.1±0.7	3.2±0.7	3.1±0.7	3.1±0.7	3.2±0.7	3.3±0.7	3.4±0.6

Global performance scale: 0=poor to 4=excellent; values are mean ±SD.

The Sponsor provided a table describing the number of patients who remained at their initial dose and the number who titrated to another dose, either higher or lower, reproduced below.

Table 11. Initial OTFC Dose Level in Relation to Last OTFC Dose Level- All Patients Reported. (Sponsor's Table 15, AC200/014)

Initial Dose(μg)	Patient Number at Each Last Dose						Pts. Finding 1600 μg ineffective*	Total No.
	200μg	400μg	600μg	800μg	1200μg	1600μg		
200	15	4	0	2	0	0	0	21
400	1	14	4	3	5	2	0	29
600	0	0	12	4	1	1	0	18
800	0	1	0	4	2	5	2	12
1200	0	0	0	0	3	1	0	4
1600	0	0	0	0	2	5	1	7
Total	16	19	16	13	13	14	3	91

*Patients in this column were also listed in the 1600 μg Last Dose column.

In the aggregate, 58% of patients remained at their initial effective dose throughout their participation. However, Table 15 does not consider time as a factor: do patients who remain the longest in the study require progressively higher doses? In order to better assess the possible development of tolerance, the

sponsors were requested to provide a summary table of monthly patient number, with initial and final doses of OTFC for each monthly group. This amendment provides initial vs final dose level on a monthly basis in a series of tables, the contents of which will be summarized here.

Month 1: 91 patients were participating. 69/88 patients (78%) did not require an increase in their dose. 3 required a decrease, 1 from an initial dose of 400 μg, and 2 from an initial dose of 1600 μg.

Month 2: 65 patients were participating. 51/65 patients (78%) remained at their initial dose. No patient participating through this time period required a reduction of dosage. Only at the 1600 μg dose did no patient (n=5) require an increase.

Month 3: 50 patients were participating. 44/50 patients (88%) remained on their initial dose. No patients required reduction to a lower dose. Out of 24 patients receiving 600, 800, or 1200 μg/dose, only one patient at each dosage level required an increase to the next higher dose. None of 9 patients at 1600 μg changed their dose.

Month 4: 37 patients were participating. 34/37 patients (92%) remained at their initial dose. No patients at 200,1200, and 1600 μg changed their dose. 2 patients increased their dose once and 1 patient increased his dose twice.

There were 25 patients participating in months 5-8 and 10 patients participating during months 9-12. 5 of these 35 patients required an increase in dosage strength. 4 patients continued to be followed for $\geq$12 months. One of 2 patients at 600μg increased to 800 μg/dose. One patient at 1200 μg and one at 1600 μg/dose remained at these doses.

In summary, for patients who remained in the study, the quality of relief achieved with Actiq did not deteriorate over time. All patients did not remain at their initial dose of Actiq, but rather were allowed to continue to titrate to a higher dose as needed. The majority of patients who participated remained at the same dose of Actiq (53/ 91 total participants, at the time of the initial filing).

8.4 Conclusions Regarding Efficacy Data

The Sponsor's clinical development plan supports the indication of Actiq for the treatment of breakthrough pain in an opioid tolerant population who are stable on long-acting opioid analgesics for chronic pain. Actiq may be titrated in each patient individually to arrive at a single-unit dose to which most episodes of breakthrough pain respond. At the effective dose, Actiq appears to be at least as