day). Pain medications at the time of hospitalization included MS Contin 120 mg twice a day for around-the-clock pain, and OTFC 1200 µg, as needed for breakthrough pain. The last dose of OTFC was taken on September 19, 1996. During this hospitalization, the urine output improved; however, the BUN remained elevated at 88 mg/dL eight days later on September 27, 1996. The investigator determined that this event was unlikely to be related to the use of OTFC.

The patient died on October 17, 1996, without being discharged. Death was due to progression of disease. Use of OTFC was not resumed after September 19, 1996. The investigator determined that this event was unrelated to be related to the use of OTFC.

Patient #42908 (AC 200/014) Withdrawal/Hospitalization

Patient #42908 was a 58-year-old white female with metastatic adenocarcinoma of the colon. She successfully completed protocol AC 200/013 (#32909) and was enrolled in extension protocol AC 200/014 on June 10, 1996. The patient was using MS Contin 120 mg twice a day for around-the-clock pain, and OTFC 1200 µg as needed for breakthrough pain. She was also treated with Decadron and Floxin (for a urinary tract infection). The patient was admitted to the hospital on September 19, 1996, for progressive loss of right arm use over the past 24 hours, which was rated as severe. On September 22, 1996, it was determined that she had developed brain metastases which were causing the loss of right arm use. She was discharged on that day to begin radiation therapy. Because the patient only used study drug once every few weeks, the last dose of OTFC prior to hospitalization was unknown, but the caregiver stated no OTFC was consumed after September 12, 1996. The investigator indicated that this event was unlikely related to the use of OTFC.

The patient experienced increasing confusion after being discharged and was re-hospitalized on October 1, 1996, for severe confusion. The caregiver stated use of OTFC had not resumed. The patient was discontinued from the study on October 8, 1996, due to her disease progression. She was discharged on October 22, 1996. The investigator stated this event was unrelated to the use of OTFC.

Patient #43103 (AC 200/014) Hospitalization

Patient #43103 was a 42-year-old white female with cervical cancer, diagnosed in November 1992. She completed protocol AC 200/013 (#33103) and enrolled in protocol AC 200/014 on May 8, 1996. Relevant medical history included radiotherapy, cisplatin and 5-fluorouridine chemotherapies, cervical biopsies, hormone replacement therapy, and placement of a left iliac stent because tumor encroachment was causing vascular compression. The patient was using MS Contin 120 mg three times a day for around-the-clock pain, and MSIR 30-40 mg as needed, or OTFC 1600 µg as needed for breakthrough pain.

On December 8, 1996, the patient experienced increased pain which became progressively worse until she was admitted to the hospital on December 10, 1996. The investigator indicated the pain was related to progression of disease. A computerized axial tomography (CAT) scan revealed slowly progressive disease in the left pelvis with bone erosion, right iliac compression, and retroperitoneal adenopathy. Severe right hydronephrosis was also present. The findings did not differ significantly from a scan done two months previously. The patient was treated with intravenous morphine via a patient controlled analgesia pump and Naprosyn. Use of OTFC was stopped while the patient was hospitalized. When discharged on December 12, 1996, the patient was using MS Contin 300 mg three times a day for around-the-clock

pain, and MSIR 30-45 mg as needed, or OTFC 1600 µg as needed for breakthrough pain. The investigator determined this event was unlikely related to the use of OTFC

Patient #43105 (AC 200/014) Withdrawal/Hospitalization
The following narrative has been revised from the ISS submission.

Patient #43105 was a 44-year-old white male with poorly differentiated adenocarcinoma of unknown primary diagnosed in April 1996. A diagnostic workup revealed a large exophytic endoesophageal mediastinal mass. He underwent radiation therapy and a gastrostomy tube was placed in April 1996. The patient completed protocol AC 200/013 (#33105) and entered AC 200/014 on August 8, 1996. The patient was using MS Contin 45 mg, twice a day, for around-the-clock control of his cancer pain, and oxycodone, 10 mg, or OTFC, 1200 µg, as needed, for treatment of breakthrough pain. The last dose of OTFC was taken August 12, 1996.

On August 8, 1996, the patient began experiencing dyspnea. On August 10, 1996, the patient was experiencing emesis and an exacerbation of dysphagia, all of which were severe enough to interfere with the patient's ability to tube feed and take his oral medications. On August 12, 1996, the patient was admitted to the hospital with a diagnosis of left lower lobe aspiration pneumonia. The patient was placed on nothing by mouth or gastrostomy tube status. His pneumonia was treated with intravenous clindamycin, erythromycin, and ciprofloxacin. He was given intravenous morphine for pain. The use of OTFC was suspended while the patient was on nothing by mouth status. **Use of OTFC never resumed because his dysphagia never improved. Dysphagia was rated by the investigator to be severe and unlikely related to study drug.**

Patient #43402 (AC 200/014) Hospitalization/Death
The following narrative has been revised from the ISS included in the original NDA submission.

Patient #43402 was a 64-year-old white male with lung cancer metastatic to bone diagnosed in April 1995. He also had a history of chronic obstructive pulmonary disease. The patient completed protocol AC 200/013 (#33403) and was enrolled in extension protocol AC 200/014 on April 11, 1996. He was using MS Contin 30 mg twice daily for around-the-clock control of his cancer pain. Percocet 1-2 tabs or OTFC 800 µg was used for treatment of breakthrough pain.

On June 12, 1996, the patient was admitted to the hospital with hemoptysis and increasing dyspnea of two days duration. There was no accompanying fever, increasing productive cough, or chest pain. The patient underwent bronchial endoscopy and was found to have progression of disease in the left lingular and lower lobe with near complete obstruction. A chest computerized tomography scan revealed possible lymphatic spread of his lung cancer. He was started on bronchodialators and external beam radiation therapy to the area of endobronchial obstruction. OTFC use was continued during the hospitalization. The patient was discharged on July 10, 1996, and began hospice care on July 15, 1996. The investigator indicated that these adverse events were unrelated to the use of OTFC.

The patient died in his home, **due to progression of his disease, on August 6, 1996.** The last dose of OTFC was taken on July 20, 1996. At the time of death, he was using intravenous morphine sulfate 2 mg per hour for around-the-clock control of his cancer pain. Intravenous morphine sulfate 4 mg every 15 minutes, Percocet 1-2 tabs or OTFC 800 µg was

used for treatment of breakthrough pain. The investigator has indicated that this adverse event was unrelated to the use of OTFC.

Patient #43403 (AC 200/014) Hospitalization/Death
The following narrative has been revised from the ISS included in the original NDA submission.

Patient #43403 was a 52-year-old white male with lung cancer metastatic to bone and liver diagnosed in December 1995. The patient completed protocol AC 200/013 (#33405) and enrolled in protocol AC 200/014 on June 11, 1996. He was using MS Contin, 30 mg twice a day, for around the clock pain, and MSIR, 15 mg as needed, or Percocet, 1-2 tablets as needed, or OTFC 1600 µg as needed, for breakthrough pain.

On August 14, 1996, the patient was admitted to the hospital for severe vomiting and uncontrolled pain, and his OTFC was discontinued at that time. When discharged on August 20, 1996, the patient's pain was additionally being treated with intravenous morphine sulfate, 2 mg continuous infusion, for around the clock pain, and intravenous morphine sulfate, 2 mg as needed, for breakthrough pain. On August 26, 1996, the patient experienced increased pain. His around-the-clock medications were increased to MS Contin, 120 mg twice a day, and intravenous morphine sulfate, 4 mg continual infusion. The bolus infusions of morphine sulfate were increased to 4 mg as needed, for breakthrough pain. The patient continued use of MSIR, 15 mg twice a day, and Percocet, 1-2 tablets as needed, for breakthrough pain. Later in the day, the patient developed an episode of grand mal seizures. The patient became progressively lethargic and unresponsive over the next three days, and died in his home, due to progression of his disease, on August 29, 1996. Use of OTFC was never resumed. The investigator determined that these events were unrelated to the use of study drug.

Patient #43602 (AC 200/014) Withdrawal/Hospitalization
The following narrative contains information on this patient from two studies, AC 200/013 and AC 200/014.

Patient #33602 was a 27-year-old white female with metastatic breast cancer. The patient was enrolled in protocol AC 200/013 on February 27, 1996. She was using Duragesic, 100 µg/hr, for around-the-clock control of her cancer pain. The patient was also using Dilaudid, 8 mg every six to eight hours, as needed, and had been titrated to 800 µg OTFC, as needed for control of breakthrough pain. In November 1995, the patient had an abscessed tooth removed, and in February 1996 she was hospitalized for an infection where the abscessed tooth had been. She was being treated at home with Clindamycin, 300 mg IV, every eight hours, for her jaw infection.

On March 19, 1996, the patient complained of nausea and vomiting, fever, and increased pain in her legs. On this day the patient had administered four 800 µg OTFC units. The following day, when the patient returned to the clinic for chemotherapy, she had a temperature of 101° F. She complained of increased pain in her legs and was markedly limping. On March 21, 1996, she presented with fever, generalized aches and a somewhat swollen jaw. She was admitted to the hospital for neutropenic fever. The patient was treated with Ceftazidime IV, Neupogen, 300 units SQ daily, and two units of packed red blood cells. The patient took her last dose of OTFC on the evening of March 21, 1996, and was then advised to suspend the use of OTFC until her fever and pain stabilized. The investigator stated that the adverse events and subsequent hospitalization were unlikely to be related to the use of OTFC. After hospitalization, the patient resumed participation in the study and successfully completed the double-blind phase.

Patient #43602 was a 25-year-old white female with metastatic breast cancer diagnosed in March 1991. She successfully completed protocol AC200/013 (#33602) and was enrolled in protocol AC200/014 on April 1, 1996. The patient was using transdermal fentanyl 100 µg per hour and ibuprofen 600 mg four times a day for around-the-clock pain. OTFC 1600 µg as needed was used for breakthrough pain.

On November 13, 1996, the patient was admitted to the hospital with a three week history of headache, two week history of confusion and agitation, and one week history of nausea and vomiting. The last dose of OTFC was taken in the evening of November 13,1996, and the patient was discontinued from the study at that time. Agitation, nausea, and vomiting persisted after discontinuation of OTFC. Cerebrospinal fluid was analyzed and showed evidence of extensive carcinomatous meningitis. An Ommaya reservoir was placed for drug administration. The patient was discharged from the hospital on November 29, 1996. The investigator has determined that these adverse events were unlikely related to the use of OTFC.

Patient #43609 (AC 200/014) Withdrawal/Hospitalization

Patient #43609 was a 60-year-old white male with metastatic prostate cancer diagnosed in June 1994. He completed protocol AC 200/013 (#33609) and was enrolled in protocol AC 200/014 on May 13, 1996. The patient was using MS Contin 75 mg three times a day for around-the-clock pain. Oxycodone 10 mg as needed or OTFC 1200 µg as needed was used for breakthrough pain.

On November 21, 1996, the patient began experiencing episodic confusion and was unable to adequately control his pain. Additionally, his family noted a marked deterioration in his oral intake. This became progressively worse during the week, and on November 28, 1996, he was admitted to the hospital with mild confusion, moderate increased pain, and dehydration. The last dose of OTFC prior to admission was taken on November 27, 1996, and he was discontinued from the study when admitted. The patient was placed on intravenous hydration and intravenous morphine 20 mg/hr for around-the-clock pain and 10 mg every 20 minutes as needed for breakthrough pain. The confusion resolved as his hydration status improved, and the patient was discharged to home hospice care on December 5, 1996. The investigator determined these events were unlikely related to the use of OTFC.
hat these events were unrelated to the use of OTFC.

Patient #43701 (AC 200/014) Hospitalization

The following narrative has been revised from the ISS included in the original NDA submission.

Patient #43701 was a 59-year-old white female with a history of rectal carcinoma diagnosed September 1995. An exploratory laparotomy and diverting colostomy were performed at that time, followed by abdominal, pelvic, and rectal radiation with chemotherapy sensitization. In December 1995, she underwent an abdominal perineal resection. The patient successfully completed protocol AC 200/013 (#33701) and was enrolled in protocol AC 200/014 on April 16, 1996. She was using MS Contin 600 mg daily for around-the-clock control of her cancer pain and Dilaudid 8 mg as needed or OTFC 1600 µg as needed for treatment of breakthrough pain. The patient was also continued on a chemotherapy regimen with 5-fluorouracil, Leucovorin, and Levamisole.

On May 1, 1996, the patient presented to her surgeon with a three day history of nausea, vomiting, abdominal distention, and pain. She was admitted to the hospital with a presumed small bowel obstruction. Her symptoms were initially managed conservatively and on May 6,

1996, an exploratory laparotomy confirmed a small bowel obstruction due to abdominal adhesions. She was discharged from the hospital on May 17, 1996. Her last dose of study drug prior to her hospitalization was taken on May 1, 1996. She didn't use OTFC during the course of her hospitalization but resumed taking study drug after her discharge. The investigator has determined that this adverse event was unrelated to the use of OTFC.

Patient #44202 (AC 200/014) Death
The following narrative has been revised from the ISS included in the original NDA submission.

Patient #44202 was a 69-year-old white male with metastatic rectal cancer diagnosed in August 1994. Upon completing protocol AC 200/013 (#34202), the patient was enrolled in protocol AC 200/014 on June 24, 1996. The patient's cancer pain had been treated with transdermal fentanyl 50 µg/hr for persistent pain. Percocet 1 tab or OTFC 600 µg as needed was used for breakthrough pain.

The patient showed decreasing consciousness beginning the morning of July 25, 1996. At 0500 hours on July 26, 1996, the patient's wife attempted to administer what would be his last dose of OTFC. Due to the patient's weakness, he was unable to suck and dissolve this last dose. The patient died at home on July 26, 1996, as a result of respiratory failure due to progression of the disease.

Concurrent medications at the time of death included Lomotil 20 mg per day, sodium chloride 1 gm per day, Chromagen 1 tab twice a day, Sandostatin 150 mcg per day, Neutra-phos 1.25 gm per day, and lidocaine, Benadryl, and Maalox as an oral solution once each day. The investigator has determined the patient's death was unrelated to the use of study drug.

Patient #44301 (AC 200/014) Withdrawal/Hospitalization/Death
The following narrative includes events that occured after the original NDA submission.

Patient #44301 was a 69-year-old white female with metastatic renal cell carcinoma, diagnosed in March, 1993. She completed protocol AC 200/013 (#34302) and enrolled in protocol AC 200/014 on June 5, 1996. The patient was using transdermal fentanyl 100 µg/hr for her around the clock pain. Percocet 2 tablets as needed or OTFC 400 µg as needed was used for breakthrough pain. The patient began experiencing severe pain in the left hip with severe muscle spasms on August 24, 1996, and was admitted to the hospital on August 25, 1996, for a pathological left hip fracture. She was withdrawn from the study on that date due to uncontrolled pain. A radiograph of the left side showed a protrusion of the left femoral head cephalad and medial. A left hip mass eroding the left iliac crest and acetabulum was also noted. The patient was placed in traction, and after failing a trial of intravenous opioids to control her pain, an epidural catheter was put in place on September 1, 1996. Her epidural infusion included fentanyl in Marcaine. The patient took her last dose of OTFC on August 23, 1996. The investigator has determined this event was unrelated to the use of study drug.

The patient died on September 21, 1996, without being discharged. The cause of death was listed as metastatic renal cell carcinoma. The investigator has stated that this event was unrelated to the use of OTFC.

Patient #44302 (AC 200/014) Hospitalization/Death
The following narrative includes events that occured after the original NDA submission.

Patient #44302 was a 48-year-old male with non-Hodgkins lymphoma, diagnosed in February 1988. He completed protocol AC 200/013 (#34303) and enrolled in protocol AC 200/014 on June 24, 1996. The patient was using Duragesic 100 µg/hr for his around the clock pain and Percocet 2 tabs as needed or OTFC 1600 µg as needed was used to treat breakthrough pain.

The patient reported to his physician's office with fever, chills, and a decrease in performance status on September 3, 1996, all of moderate severity. He was scheduled to receive chemotherapy and was admitted to the hospital at that time, for potential support during the chemotherapy. The patient continued to use OTFC during the hospitalization. The patient was discharged on September 7, 1996. The investigator determined these events were unrelated to the use of study drug.

On September 14, 1996, the patient was admitted to the hospital with severe stomatitis, moderate pancytopenia, moderate wasting, moderate dehydration, and moderate increased pain associated with swallowing, all secondary to chemotherapy. Blood cultures drawn on September 15, 1996, grew Streptococcus viridans, Captocytophago, and Candida albicans. The patient was treated with Unasyn 1.5 gm, Nizoral 200 mg daily, Zovirax 800 mg twice a day, intravenous clindamycin 300 mg every 8 hours, and intravenous amphotericin B 30 mg daily. OTFC was used on September 14, 1996, and was not used again until September 29, 1996. He was discharged on September 30, 1996.The investigator determined these events were unrelated to the use of OTFC.

The patient was admitted to the hospital on October 19, 1996, with a moderate fever, mild pleural effusion, decreased hemoglobin and hematocrit, and wasting. He completed a course of chemotherapy the day before admission. The last dose of OTFC prior to admission was on October 15, 1996. He was treated with intravenous Diflucan 400 mg daily, Claforan 1g every 8 hours, Neupogen (G-CSF) 480 µg daily, and Nystatin swish and swallow 5 cc four times daily. When discharged on October 22, 1996, the patient remained on intravenous Diflucan, 400 mg daily. Use of OTFC continued. The investigator determined these events were unrelated to the use of study drug.

On November 8, 1996, the patient was hospitalized for a thoracentesis due to increased pleural effusion and for Groshong catheter placement. His condition continued to deteriorate over the next three days, and the patient died as a result of his disease progression on November 13, 1996. The last dose of OTFC prior to death was taken on November 5, 1996. The investigator determined these events were unrelated to the use of OTFC.

Patient #44401 (AC 200/014) Withdrawal/Hospitalization
The following narrative includes events that occured after the original NDA submission.

Patient #44401 was a 47 year-old male undergoing chemotherapy for metastatic gastric adenocarcinoma. The patient completed protocol AC 200/013 (#34402) and entered AC 200/014 on May 8, 1996. The patient was using Duragesic 200 µg per hour for around-the-clock control of his cancer pain, and hydromorphone 4 mg as needed or OTFC 600 µg, as needed for treatment of breakthrough pain. During the course of the study, the patient was

titrated up to Duragesic 400 µg and OTFC 1200 µg for control of his around-the-clock and breakthrough pain respectively.

On July 8, 1996, the patient presented to the emergency room with a fever and cough. He was admitted to the hospital on that date with a diagnosis of leukopenia and pneumonia. His pneumonia was treated with intravenous vancomycin, gentamicin, and Fortaz. The patient continued to use OTFC throughout the hospitalization. The patient was discharged on July 11, 1996, and finished his course of intravenous antibiotics at home. The investigator states that this event was unrelated to the use of study drug.

On September 30, 1996, the patient began complaining of increasing pain and was placed on a subcutaneous Dilaudid pump. On October 3, 1996, the decision was made to withdraw the patient from the study as his pain had increased and was now being controlled by the subcutaneous pump. The patient consumed his last dose of OTFC on that day. The investigator has indicated that the increasing pain experienced by the patient was unrelated to the use of OTFC.

Patient #44601 (AC 200/014) Hospitalization

Patient #44601 was a 42-year-old white female diagnosed with breast cancer in June 1988. She completed protocol AC 200/013 (#34601) and entered protocol AC 200/014 on July 18, 1996. Her medical history was also significant for hypothyroidism and diabetes mellitus. The patient was using MS Contin 45 mg four times a day for around-the-clock pain, Klonopin 0.5 mg three times a day for neuropathic pain, baclofen 10 mg three times a day for cancer related joint pain, ibuprofen 600 mg three times a day for bone pain, and OTFC 400 µg as needed for breakthrough pain.

The patient underwent Taxol chemotherapy on October 4, 1996, and began experiencing nausea and vomiting that day. All oral medications were discontinued on October 7, 1996. On October 8, 1996, she was admitted to the hospital for post chemotherapy intractable nausea and vomiting and was placed on a one day regimen of intravenous morphine. The nausea and vomiting were rated as severe. It was later determined that she also had a concurrent gastrointestinal viral infection. The last dose of OTFC prior to hospitalization was September 17, 1996, due to decreasing pain, and further use of OTFC was suspended until her condition stabilized. The patient was discharged on October 12, 1996. The investigator determined these events were unrelated to the use of OTFC.

Patient #44702 (AC 200/014) Withdrawal/Hospitalization

Patient #44702 was a 58-year-old white female with metastatic breast cancer diagnosed in March 1993. She successfully completed protocol AC 200/013 (#34704) and enrolled in protocol AC 200/014 on May 29, 1996. She was using MS Contin 60 mg three times a day for around-the-clock pain, and MSIR 15 mg as needed or OTFC 800 µg as needed for breakthrough pain.

On July 22, 1996, the patient was hospitalized for intractable pain due to disease progression. She was placed on intravenous morphine, and titrated to 43 mg/hr over the next 4 days. Use of OTFC was suspended during the hospitalization. The intravenous line was discontinued on July 26, 1996. When discharged on July 27, 1996, she was using MS Contin 180 mg every 8 hours for around-the-clock pain and OTFC 1200 µg as needed for breakthrough pain. The investigator stated this event was unrelated to use of OTFC.

On September 3, 1996 the patient began complaining of a marked increase in pain. Her MS Contin was discontinued and she was again placed on intravenous morphine titrated to 35

mg/hr over the course of the next three days. Prior to this day, her dose of MS Contin had been increased to 400 mg every 8 hours. On September 7, 1996, the decision was made to withdraw the patient from the study due to disease progression and increasing pain. The patient's last dose of OTFC was consumed on this day. The investigator has determined that this event was unrelated to the use of OTFC.

4.6.1 Narratives - Patients Participating in Study AC 200/015

Patient #4711 (AC 200/014) Hospitalization
Patient #4711 was a 72-year-old white male with prostate cancer diagnosed March 29, 1991, and metastatic non-small cell lung cancer diagnosed January 26, 1996. He successfully completed protocol AC 200/015 (#5702) and was enrolled in protocol AC 200/014 December 19, 1996. The patient was using transdermal fentanyl 125 µg/hr for around-the-clock pain, and Percocet two tabs as needed or OTFC 600 µg as needed for breakthrough pain. The patient had developed seizure activity in 1995 due to disease progression and treatment. He had undergone a frontal craniotomy with debulking of a cranial and epidural tumor. His immediate post-operative course was complicated by status epilepticus. He was using Tegretol 200 mg four times a day.

At approximately 1540 on January 12, 1997, the patient experienced a severe grand mal seizure. He was admitted to the hospital later that day for observation. The patient was initially comatose, only slightly responsive to voice and touch stimulation, and had Todd's paralysis following the seizure. A feeding tube was placed for medication administration and nutritional support, and the patient was discontinued from the study at that time. The last dose of OTFC 600 µg was taken at 1000 on January 12, 1997. The patient was discharged to an extended care facility on January 15, 1997. The investigator indicated this event was unrelated to the use of OTFC.

Patient #42609 (AC 200/014) Withdrawal/Hospitalization/Death
Patient #42609 was a 54-year-old white male with colon cancer diagnosed in 1993. The patient completed protocol AC 200/015 (#52601) and enrolled in protocol AC 200/014 on October 1, 1996. He was using Duragesic 100 µg/hr for around-the-clock pain. Dilaudid 1 tablet as needed or Demerol 50 mg as needed or OTFC 800 µg as needed was used for breakthrough pain.

The patient noticed mild blood in his urine and moderate blood in his colostomy on December 12, 1996, and was admitted to the hospital the following day. An endoscopy was done and no abnormal findings were noted. The patient was treated with two units of packed red blood cells. The hematuria and hematochezia resolved. Use of OTFC continued while he was hospitalized. He was discharged on December 15, 1996. The investigator indicated this event was unrelated to the use of OTFC.

On December 26, 1996, the patient was admitted to the hospital with moderate intestinal leakage into his bladder. Due to the advanced state of his disease, no treatment was undertaken. Use of OTFC continued while hospitalized. He was discharged on December 31, 1996. The investigator determined this event was unrelated to the use of OTFC.

On January 2, 1997, the patient was unable to urinate, and was admitted to the hospital with severe kidney failure. A sonogram performed on that date showed massive tumor invasion. The last dose of OTFC 800 µg was on January 1, 1997, and the patient was discontinued from the study at that time. His kidneys had begun to function minimally on January 7, 1997. The

patient died on January 11, 1997, without being discharged. The investigator determined this event was unrelated to the use of OTFC.

Patient #43101 (AC 200/014) Hospitalization/Death

Patient #43101 was a 41-year-old white male with metastatic synovial cell sarcoma diagnosed in December 1987. He has undergone surgical wedge resections of metastatic lesions to the lung [1992 (2), 1993] and to the liver (1992). He received chemotherapy in 1991 and 1992 and underwent radiation therapy for spinal cord compression in February 1995, February 1996, and most currently in July 1996. The patient completed protocol AC 200/015 (#51502) and entered protocol AC 200/014 on April 25, 1996. He was using MS Contin 15 mg twice a day for around-the-clock pain, and OTFC 400 µg as needed for breakthrough pain. The patient had a history of intermittent shortness of breath since February 1996. In June 1996, he was treated with a three week course of prednisone therapy for suspected radiation pneumonitis and had a stable respiratory status when evaluated on July 5, 1996 and August 5, 1996. A slight increase of exertional dyspnea was noted on September 3, 1996.

On October 4, 1996, the patient presented with abdominal pain and bloating of approximately two weeks duration and increased shortness of breath which had worsened that day. All the events were rated as being moderate. He was admitted that evening for evaluation of the abdominal pain. The last dose of OTFC prior to hospitalization was at 0400 on October 4, 1996. The abdominal workup was negative. The investigator stated that the abdominal pain was unlikely related to OTFC. A new pulmonary metastasis was found, and he was diagnosed with a post-obstructive right lower lobe pneumonia with referred pain to the abdomen. The patient was placed on oxygen and intravenous erythromycin 500 mg every six hours, ceftaxim 2 g every eight hours and trimethoprim/sulfamethoxazole 400/2000 mg every six hours for his pneumonia. The patient's MS Contin was increased to 30 mg twice a day. The patient's abdominal distress resolved and respiratory status was stable on October 5, 1996. OTFC remained available to the patient.

On October 6, 1996, the patient received OTFC at 0600 and 1030. He experienced shortness of breath again on this day, and at 2000 he was transferred to the trauma life support center for increased ventilatory support with continuous positive airway pressure (CPAP). The patient was placed on hold from the study following his last dose of OTFC at 1100 on October 7, 1996. All oral medications were discontinued on October 8, 1996, when he was emergently intubated. In addition to antibiotics, the patient was placed on intravenous morphine. The patient was expected to resume use of OTFC when his condition stabilized. The patient's respiratory status continued to deteriorate. He died on October 11, 1996, due to progression of his disease, without being discharged. Use of OTFC was not resumed. The investigator stated that the hospitalization was unlikely related to the use of OTFC, and the death was unrelated to the use of OTFC.

20-747

JAN 28 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION of ANESTHETICS, CRITICAL CARE and ADDICTIVE DRUGS

FINAL STUDY REPORT

NDA: 20-747

Product: Oral Transmucosal Fentanyl Citrate
Sponsor: Anesta

Submission: commercial **Protocol #:** AC 200/013
Title: A Multicenter, Double-Blind, Placebo Controlled Crossover Study of Oral Transmucosal fentanyl Citrate(OTFC) for the Treatment of Breakthrough Pain in cancer Patients taking Stable Doses of Opioids

Date of Review: 1/24/97

CSO: M. Wright
Medical Reviewer: Roberta C. Kahn, M.D.

This study is one of the pivotal clinical studies for support of this NDA. The purpose of the study is to demonstrate the efficacy of OTFC as an analgesic for breakthrough episodes of pain in cancer patients who are taking opioids chronically for pain. The study examined whether patients could achieve an effective dose of OTFC by titration, and subsequently compared the effect of that dose to placebo.

Study Outline: This was a multicenter, double-blind, placebo-controlled, crossover study of patients taking stable around-the-clock opioid therapy for chronic cancer pain, and who also required therapy for episodes of breakthrough pain. 130 patients, age 20-84 years, entered the first phase of the study, in which an effective dose of OTFC was identified by titration through the available dosage strengths (200-1600μg). 93 patients titrated to a single dosage strength that provided pain relief for breakthrough episodes. 92 of these patients entered the double blind phase, in which they each received 10 pre-numbered OTFC units, of which 7 were their effective dose and 3 were placebo. Patients were asked record pain intensity, pain relief, global performance of the treatment, and adverse events.

Clinical Plan: Patients were eligible to participate who were taking 60-1000 mg of morphine or 50-300 μg/hr transdermal fentanyl for pain associated with cancer or cancer treatment, and experiencing 1-4 episodes of breakthrough pain/day. At the start of the dose titration phase, up to 6 units of each dosage strength (200, 400, 600, 800, 1200, 1600 μg) were dispensed to the patient. The patient was instructed to start with the 200 μg dose. For each episode the patient self-administered one OTFC unit; if pain relief was insufficient, an additional unit, up to a total of 4 units, could be administered. Patients were instructed to wait 15 minutes after completion of each OTFC unit, and 2 hours between treating any

subsequent episode of pain. The need for more than one unit to treat an episode was an indication to increase to the next higher dosage strength; the dose was decreased for excessive adverse effects.

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. Patients in this phase continued to use one OTFC unit for each episode of breakthrough pain. The patient received 10 randomized prenumbered units, of which 3 were placebo, 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: treatment of 10 episodes in 14 days. 7 patients withdrew due to an adverse event, 13 patients withdrew for other reasons. 4 adverse events were considered unrelated to OTFC by the investigator.

For each episode of pain, the patient rated the following variables:

- 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) (please see review of AC200/010 for definitions of these variables). 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.

Statistical Methods: 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.
- COSTART adverse events: exact binomial distribution, 90% upper confidence bound.

For more detailed discussion of statistical methods, please see the Statistician's Review.

Results: 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 ($p = 0.57$). 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. This finding appears to be consistent across the sponsor's clinical studies in which OTFC is used in addition to around-the-clock morphine or fentanyl (AC200/011, AC200/012, AC200/013, AC200/014).

Efficacy variables (evaluable patients): PI, PID, SPID, PR, and TOTPAR scores were lower for OTFC compared to placebo at 15 minutes and all subsequent time points. These differences were significant ($p<0.0001$). 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.

Safety variables: 93 of 130 patients completed the titration phase. 22 withdrew because of adverse events, and 15 withdrew for other reasons. 92 patients agreed to enter the double blind phase. 7 withdrew due to adverse events, and 13 withdrew for other reasons. The adverse events reported by the investigators as related to OTFC were as follows (number of patients):

Titration phase:

- dyspnea/death - possibly related (1)
- nausea/vom/diarrhea/dehydration - possibly related (1)
- nausea - possibly related (4)
- dyspnea/dizziness/sweating - possibly related (1)
- hallucinations/confusion - possibly related (1)
- dizziness - possibly related (1)
- vomiting - related (1)

Double-blind phase:

- itching/urticaria - possibly related (1)

There did not appear to be a relationship between occurrences of adverse events and increasing the dose of OTFC. 65% of total patient withdrawals occurred during titration at the four lowest doses of OTFC: 200, 400, 600, 800 μg.

Overall, in both phases of the study, nausea was the most common adverse event, reported in 33% of cases. Nausea was judged by the investigator to be related to OTFC ingestion in 14% of cases, and unrelated to the study drug in 19% of cases. Dizziness occurred in 22% of patients, asthenia and vomiting were each reported at 19%.

There were no reports of respiratory depression. However, respiratory depression cannot be observed as a subjective symptom. The pharmacodynamics of fentanyl predicts that somnolence would invariably be accompanied by some degree of respiratory depression. Somnolence was reported in 16 patients, and was observed at a variety of dosage strengths: 200μg (5 cases), 400 μg (3 cases), 600 μg (2 cases), 800 μg (3 cases), 1600 μg (3 cases). 28 patients experienced dizziness, 7 patients experienced confusion, 5 patients experienced abnormal thinking or hallucinations, 1 experienced euphoria, 7 experienced, abnormal gait, vertigo, or incoordination. 2 patients injured themselves in association with OTFC use.

Eight deaths during the study were reported as related to progression of disease;

none apparently were related to the use of OTFC.

Discussion:

This study was conducted in the target population of patients: opioid-tolerant cancer patients experiencing breakthrough pain. The majority of patients were able to find a dosage strength of OTFC which was effective for treating breakthrough pain, while also using a long-acting morphine or fentanyl preparation. The range of effective doses was 200-7200 μg. No relationship could be consistently established between the effective dose of OTFC and the "background" dose of morphine or transdermal fentanyl.

Patients noted the onset of pain relief within 15 minutes of the beginning of administration of OTFC. OTFC was more effective than placebo; however, 65% of episodes treated with placebo were not treated with other rescue medication, possibly because of the limited duration of breakthrough pain episodes.

The investigation supports the technique of allowing the patient to self-titrate through the available dosage strengths, balancing effectiveness against undesirable adverse effects. While the most common side effect was nausea, the potential for adverse events such as somnolence, dizziness, vertigo, incoordination, confusion, and hallucinations suggest that specific warnings about a safe environment during the use of OTFC are needed, at least until the patient arrives at an effective and well-tolerated dose.

/S/

Roberta C. Kahn, M.D. — Date 1/28/97

/S/ X

Peer Reviewer — Date 1/28/97

NDA 20-747
HFD-170 Div. File/ M. Wright/ R. Kahn/ L.Landow

20-747

MAR 3 1997
Dr. File

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION of ANESTHETICS, CRITICAL CARE and ADDICTIVE DRUGS

FINAL STUDY REPORT

NDA: 20-747

Product: Oral Transmucosal Fentanyl Citrate
Sponsor: Anesta

Submission: commercial **Protocol #:** AC 200/014
Title: An Open-label, Long -term, Multicenter Study of Oral Transmucosal Fentanyl Citrate (OTFC) for the Treatment of Breakthrough or Incident Pain in Cancer Patients Previously Enrolled in Other OTFC Studies

Date of Review: 2/18/97

CSO: M. Wright
Medical Reviewer: Roberta C. Kahn, M.D.

This study is an interim analysis of a multicenter, open-label, long-term study conducted to demonstrate the safety and tolerance to OTFC in the dosage range of 200-1600 μg for breakthrough episodes of pain in patients who are chronically tolerant to opioids. The study population was recruited from cancer patients who had participated in one of the previous titration studies of OTFC (AC200/011, 200/012, 200/013, 200/015).

Study Outline: This 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.

Clinical Plan: Patients were instructed to use no more than 6 OTFC units per day, for no more than 4 episodes per day. This stipulation was subsequently amended to allow 4 episodes per day *on average* to be treated, and removed the restriction to use of OTFC

during waking hours only. Also, amendments were filed to allow the use of both lemon-flavored and raspberry flavored OTFC units, and to allow patients from AC200/013 to participate without additional laboratory tests, and to allow patients from AC200/015 to participate by undergoing an initial dose titration phase for OTFC for the breakthrough pain indication.

Because this report is an interim analysis, an arbitrary cut-off date ofJuly 15, 1996 was chosen. Data from completed four-month blocks, and for patients who withdrew by that date were included. Patients are categorized on the case report forms as: Ongoing; Completed, Did not re-enroll; Withdrew, adverse event; Withdrew, other reason.

Statistical Methods: Long-term safety data, efficacy, and dosage level were summarized descriptively, and statistics were not applied. For safety data, the exact binomial distribution was calculated to identify the 90% upper confidence bound for each COSTART adverse event reported.

Results:
As of July 15, 1996, 147 patients were enrolled. For this interim report, 94 patients had completed at least one four-month block or had withdrawn from the study, with a breakdown as follows:

19 patients completed at least one 4-month block
8 patients completed one block and did not re-enroll
38 patients withdrew due to an adverse event
29 patients withdrew for other reasons

There are 53 ongoing patients who are not included in this report.

Safety variables: 38 patients withdrew due to adverse events, of which 28 were considered to be unrelated to OTFC. Cases of death due to progression of disease were reported as "unrelated" in some cases and "unlikely related" in others. No adverse events were reclassified in this review.

"Unrelated"

Death due to disease progression:	11
Death due to aspiration of mucus plug	1
Difficulty swallowing	1
Weakness	4
Increased or uncontrolled pain	4
Progression of disease	1
Abdominal distension, confusion	1
Vision changes	1
Altered mental status	3
Leukopenia	1

"Unlikely related:"

Death due to disease progression	2
Shortness of breath	1
Nausea	1
Mouth swelling	1
increased pain, weakness	1

"Possibly related:"

nausea/vomiting	2
dizziness	1
pruritis/rash	1

Withdrawals for reasons other than adverse events included patient relocation, decrease in pain, inability to achieve effective dose, and dissatisfaction with drug effect or the burden of study requirements.

One patient who was supposed to receive 200 μg/unit inadvertently received 1600 μg/unit due to a pharmacy error. The patient used these units until the error was discovered 9 days later. The patient experienced behavior changes which were considered unrelated to OTFC, and otherwise no other evidence of toxicity.

Other adverse events that did not lead to withdrawal but were temporally related to OTFC use were: nausea (5 cases), nausea/vomiting (1), vomiting (3), dizziness (9), somnolence (9), constipation (4), depression (2), myoclonus (2). Other adverse events (1 case each) were: asthenia, headache, anorexia, oral thrush, rectal disorder, dry mouth, abnormal dreams, abnormal thinking, nervousness, vasodilatation, sweating, taste perversion.

Other adverse events of significance that were considered unrelated to OTFC use were: accidental injury (4), chest pain (10), confusion (6), abnormal gait (3), abnormal thinking (3), hallucinations (2), abnormal vision (5), and stupor (3). The judgement of that these adverse events are unrelated to OTFC is based only on whether OTFC was consumed the same day.

There were no reports of respiratory depression. However, respiratory depression cannot be observed as a subjective symptom. The pharmacodynamics of fentanyl predicts that somnolence would invariably be accompanied by some degree of respiratory depression (reviewer's comment).

Three patients who were hospitalized for an adverse event had blood drawn for serum fentanyl concentration, in an attempt to identify a potential relationship. In two cases the fentanyl level was subtherapeutic (1.7 and 0.97 ng/ml), and in one case, where the patient's around the clock medication was transdermal fentanyl, the level was in the therapeutic range (5.0 ng/ml).

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

Summarized from Sponsor's Table 20

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 table suggests that, for patients who remained in the study, the quality of relief achieved with OTFC did not deteriorate over time. All patients did not remain at their initial dose of OTFC, 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 OTFC (53/ 91 total participants).

Discussion:
This study was conducted in the target population of patients: opioid-tolerant cancer patients experiencing breakthrough pain. The majority of patients were able to find a dosage strength of OTFC which was effective for treating breakthrough pain, while also using a long-acting morphine or fentanyl preparation. The range of effective doses was 200-7200 μg. No relationship could be consistently established between the effective dose of OTFC and the "background" dose of morphine or transdermal fentanyl. This finding is in contrast to the general clinical observation with other rescue analgesics that a proportionality between the effective dose of rescue analgesic and around-the-clock analgesic requirement can be identified. Nevertheless, the failure to observe a proportional relationship between the dosage requirements of OTFC and around-the-clock analgesic has been consistent among the studies in this IND. While there is no explanation offered by the sponsor for this phenomenon, the sponsor's intends to label OTFC with the recommendation to titrate from the lowest dosage strength until the effective dose is reached. The experience in this study, and the earlier titration studies supports this approach as a safe technique for OTFC.

In this interim analysis, approximately 40% of patients remained in the protocol for a four month block, and less than one third by the eighth month. Deaths in this series were attributable to progression of disease, and were not precipitated by the use of OTFC. The side effects most often encountered were nausea, dizziness, somnolence, constipation and vomiting. These adverse events are characteristic effects of all opiate drugs. In 4 cases, the side effects of OTFC were cited as the reason for patient withdrawal. In general, OTFC was used extensively and safely by the study population The central nervous system side effects: dizziness, somnolence, thought disorder, depression, abnormal dreams will require appropriate precautionary labeling and instructions to patients.

/S/

Roberta C. Kahn, M.D. — Date 3/3/97

/S/

Peer Reviewer — Date 3/3/97

NDA 20-747
HFD-170 Div. File/ M. Wright/ R. Kahn/ L.Landow

ABUSE LIABILITY ASSESSMENT REVIEW

NDA: #20-747

Drug: Actiq (Oral Transmucosal Fentanyl Citrate)

Dosage Form: Lozenge on a stick

Dose: 200 µg, 400 µg, 600 µg, 800 µg, 1200 µg and 1600 µg

Sponsor: Anesta Corporation

Date Submitted: 11-11-96

Reviewer: Michael Klein, Ph.D.

Date: June 13, 1997

Proposed Indication: For management of chronic pain, particularly breakthrough pain, in patients who are already receiving and are tolerant to opioid therapy.

Related Submission: Oralet (NDA 20-195) 100, 200, 300, 400 µg. Indicated for in-hospital use as an anesthetic premedication or for inducing conscious sedation prior to a diagnostic or therapeutic procedure in a monitored anesthesia care setting.

Supporting Submissions: IND (OTFC); DMF Fentanyl Citrate ; DMF Artificial Raspberry Flavor #906.014/WC DMF Plant Master File (Abbott Laboratories, North Chicago, IL).

Abuse Liability & Overdosage Information

The Sponsor's abuse liability assessment package included the following: literature articles describing clinical drug abuse assessment studies of fentanyl substance, clinical comparison of pharmacodynamic properites of the OTFC versus parenteral products, and assessment of pharmacokinetic parameters from administration of excess OTFC product simultaneously and comparison with those of parenteral products.

1. Active pharmacological agent is a CII narcotic.

   a. Sponsor maintains that the abuse risk of OTFC dosage form is no greater than and probably less than that presented by other marketed µ-agonist analgesics.

   b. Sponsor maintains that the drug's slow-onset PK and PD, relative to that of injected opioids make OTFC relatively unattractive to drug abusers. At the same time, the Sponsor maintains that the rapid analgesic relief to chronic pain patients, is a benefit that far outweighs the risks of abuse. Both availability and PK/PD issues of the drug are relevant.

   c. Sponsor proposes that the product (which contains the CII opioid fentanyl), be controlled in the most restrictive schedule of the Controlled Substances Act for approved drugs, that is, as a CII narcotic, as are all other fentanyl products.

   d. General Characteristics of Fentanyl: Opioid (µ-receptor) agonist of known high abuse liability when administered intravenous.

Pharmacological profile is similar to that of morphine, but with greater potency and shorter duration of action.

f. Primary use is as intravenous analgesic, sedative and anesthetic before and during surgery and for postoperative pain.

g. Abuse occurs primarily by injection and among health care professionals who have access to the injectable drug product in their workplace. This is relative to availability, however. There has been recent abuse of the fentanyl patch reported, involving either extraction or vaporization and inhalation of the fentanyl. Abuse of fentanyl (or fentanyl analogs) has also been reported to occur among "street drug abusers" (1980's). The latter typically involves drugs illicitly manufactured in clandestine labs and known as "China White"; abuse of these fentanyl products has also been generally by intravenous route. All of this supports the CII opioid recommendation - strictest level of control.

h. Drug Abuse Clinical Pharmacology of Injected Fentanyl- Methods for assessing and characterizing the abuse liability of opioids include assessing the profile and time course of subjective, physiological and observer-rated effects following challenge administration to experienced opioid abusers. In such studies, test challenges have generally been administered by the s.c. or i.m. routes.

i. Intramuscular Fentanyl- Drug abuse clinical pharmacology was assessed by these methods (Gorodetzky & Martin), who concluded that fentanyl was a morphine-like drug of abuse with a potency 25-50 times that of morphine but with a shorter duration of action; the magnitude of fentanyl effects decreased by the 2nd hour post-injection, while those of morphine did not decrease until after the 4th hour. By this route, 400-800 µg fentanyl was approximately equivalent to 20 mg morphine.

j. Zacny *et al.* tested intravenous doses of 0, 25, 50 and 100 µg/70 kg in normal volunteers without histories of drug dependence. All 3 active doses produced significant dose-related elevations in ratings of subjective "high". However, they also produced significant elevations on other subjective ratings which often times provides conflicting interpretation such abuse liability data. For example, ratings of "Sick" increased, LSD scale scores increased, ratings of "Liking" of drug effect also revealed a mixed picture. Both the 50 and 100 µg doses produced brief significant elevations in the opposite direction to "disliking", remaining for 2-1/2 hrs. Authors concluded normal volunteers provide an insensitive index of abuse liability, and many normal individuals may like fentanyl to some extent on initial exposure and that such a response might increase the risk for drug abuse.

k. Greenwald *et al.* evaluated intravenous fentanyl (0, 125, 250 µg/70 kg) in experienced opioid abusers who were currently non-dependent. Both active doses produced significant elevations on ratings of subjective "high", "liking", and "good drug effect", and on scores on an adjective rating scale of opioid symptoms associated with opioid abuse liability. Both the Zacny & the Greenwald studies reported peak subjective effects to occur within the first 5 minutes following intravenous administration. Shafer *et al.* published PK parameters of fentanyl and an equilibrium $t_{1/2}$ (equilibrium between plasma and brain) of 4.7 minutes and predicted that peak brain concentration of fentanyl occurs 3.6 min. after a bolus injection, consistent with Greenwald.

1. Overall, fentanyl elicits a profile of rapid-onset euphoric subjective efects associated with parenteral administration.

2. Unaltered OTFC Product

a. Comparative transmucosal and intravenous PD data were presented.

b. Time course of response by normal volunteers on an adjective checklist of items reflective of opioid agonist effects associated with abuse liability following 3 separate administrations of a single 800 µg OTFC. Peak subjective effects occurred 30-60 minutes after oral transmucosal administration; intravenous response occurred at 0-15 min.

c. Direct testing of OTFC in experienced opioid drug abusers was not conducted. It was not demonstrated whether OTFC delivers sufficient fentanyl to be euphoric or rewarding to drug abusers. Sponsor proposes that OTFC doses of 400-800 µg or higher would, in non-tolerant individuals, produce the type of subjective effects sought by opioid drug abusers.

d. Iatrogenic Drug Abuse Issue: Sponsor provides a published letter (Porter & Jick 1980) to minimize importance of iatrogenic addiction developing with this drug. This is dated, not relevant and minimal data was cited. However, labeling and regulation of OTFC as a CII narcotic would be expected to be sufficient to reduce this risk.

e. Risk of diversion: Abuse of injectable fentanyl by drug abusing health care professionals occurs primarily via diversion. Sponsor maintains that OTFC presents a relatively low risk for such illicit diversion by drug abusing health care professionals. No reviewable risk data was presented to support this premise, however.

h. Risk of Extraction from OTFC: Sponsor states that it is possible that abusers might attempt to extract fentanyl from the OTFC and inject the resulting fentanyl solution. Sponsor considers it unlikely to be a common or significant problem since it would be an "inconvenient, cumbersome, and expensive source of fentanyl." Still such occurrences have been reported to MedWatch for Duragesic (fentanyl transdermal patch). Sponsor did not address abuse by young people and the drug's appeal to young people, as a candy and as a drug abuse.

i. Abuse of legitimately-manufactured fentanyl is a problem seen primarily in health care professionals who have access to fentanyl products in the workplace. Those are the individuals who have access to the drug and abuse it, although quantitative assessment was not provided.

j. The Sponsor has "failed to detect any cases of abuse by health care professionals. As of the last quarter 1996, very few numbers of dosage units of the product, *Fentanyl Oralet* (intended for in-hospital use as a premedication before surgery and painful procedures), were in fact distributed, and there were no reported cases of abuse. Nor would it be anticipated that such abuse would be uncovered with such low availability. The Sponsor noted that 25,000 units of OTFC were administered in clinical studies in chronic pain patients treated primarily as outpatients, again with no reports of abuse. Rarely is abuse data reported in clinical efficacy trials.

NUMBERS OF DOSAGE UNITS OF ORALET (OTFC) DISTRIBUTED IN USA FOR 1995 AND 1996

YEAR	UNITS	EACHES	EXTENDED UNITS
1996	---		LOZENGES
1995		-	LOZENGES

UNITS = NUMBER OF SHIPPING PACKAGES
EACHES = NUMBER OF PACKAGES IN THE SHIPPING PACKAGE (5 EACHES/UNIT)
EXTENDED UNITS =NUMBER OF LOZENGES PER EACHES (5 PER UNIT X 5 UNITS = 25)

SOURCE:
CATEGORY REPORT, ON-LINE.

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k. However, Duragesic, a fentanyl transdermal product that has a wider marketing distribution (at retail level) than the injectable product, is a better comparator. See chart below containing IMS retail prescription data for Duragesic as compared with parenteral fentanyl products. Duragesic also has the problem with disposal of product while still containing considerable amounts of active drug.

PROJECTED TOTAL RX'S DISPENSED BY RETAIL PHARMACIES (CHAIN, INDEPENDENT, FOOD STORE & MAIL ORDER) IN USA FOR FENTANYL CONTAINING PRODUCTS, FIRST QUARTER 1997 & ANNUALLY 1991-1996 (IN THOUSANDS)

PRODUCT	1997 1st Qtr	1996	1995	1994	1993	1992	1991
DURAGESIC	208	805	682	524	496	343	126
FENTANYL INJ (WYETH)	1	4	2	2	4	3	1
FENTANYL INJ (ABBOTT)	*	2	*	*	*	*	
SUBLIMAZE	*	1	1	2	3	3	3
FENTANYL INJ (SANOFI WINTHROP)		*	*				
ORALET	*	*					
INNOVAR (COMBO WITH DROPERIDOL)			*	*	*	*	

"*" MEANS PROJECTED TOTAL NUMBER OF PRESCRIPTIONS DISPENSED WAS LESS THAN 500 (BETWEEN 1 & 500) AND A "BLANK" MEANS NO DATA WAS AVAILABLE.

Duragesic ADRs (Nerabuse Costart terms) reported (1989 to March 1997) are as follows:

		# COUNTS	RANKING
1.	DRUG DEPENDENCE	35	4
2.	DRUG DEPENDENCE/ADDICTION	7	16
3.	EUPHORIA	11	12
4.	HALLUCINATIONS	79	1
5.	OVERDOSE	34	5
6.	OVERDOSE ACCIDENTAL	10	13
7.	OVERDOSE INTENTIONAL	10	13
8.	SUICIDE ATTEMPT	15	10
9.	TOLERANCE INCREASE	59	2
10.	WITHDRAWAL SYNDROME	51	3

OTHER COSTARTS: NO DRUG EFFECT (#27; 6), CONFUSION (#23; 7), SOMNOLENCE (#22; 8), AGITATION (#16; 9), TREMOR (#16; 9), NERVOUSNESS (#15; 10), HYPOVENTILATION (#14; 11), INSOMNIA (#11; 12).

NUMBER OF MEDWATCH REPORTS FOR DURAGESIC BY YEAR:

	YEAR	TOTAL#	#SERIOUS	#DIED
1.	1989	7	1	1
2.	1990	1	0	0
3.	1991	22	6	5
4.	1992	39	21	12
5.	1993	76	17	11
6.	1994	31	12	8
7.	1995	52	22	8
8.	1996	56	18	13
9.	1997	2	1	0
	TOTAL	286	98	58

NUMBER OF CASES PER SERIOUS OUTCOME, BY SUSPECT & OTHER DRUG:

	TOTAL CASES	TOTAL SERIOUS	TOTAL DIED
DURAGESIC	252	81	54
FENTANYL	36	19	5
SUBLIMAZE	1	1	1

Descriptions of several of the above cases reported to MedWatch included:

1. Individual who chewed on a 5 mg patch.
2. Individual took the partner's patch and "smoked it".
3. Individual scraped gel from six patches, recrystallized drug and smoke the drug in a pen cartridge.
4. Several individuals with drug abuse histories.
5. Piece of patch found in gastric contents.
6. Individual took 5 x 50 MU patches at one time.
7. Drug was used by mistake.
8. Child chewed father's drug product that had been discarded in trash

1. Multiple Dosing with OTFC Units: Sponsor maintained that thedesign of OTFC reduces the number of dosage units which an adult abuser could fit in the mouth without cutting off the handle. Eleven dosage units could be taken at one time, which seems improbable. The ease of using the drug to maintain an opiate addiction, however, was not addressed by Sponsor.

m. PK Study Conducted:

i. If an abuser tries to consume 5 units concurrently, handles attached: Using the maximum dosage form of 1,600 µg and a 15 minute dissolution time, the total amount of drug administered would be 8 mg/15 minutes.

ii. If an abuser tries to consume 11 units concurrently, handles removed: Using the maximum dosage form of 1,600 µg and a 15 minute dissolution time, the total amount of drug administered would be 17.6 mg per 15 minutes.

iii. C_{max} worst case scenarios estimates:

Observed Study Data:

Route	Dose(µg)	Dose(µg/kg)	Cmax(ng/ml)
OT	200	2.6	0.39
OT	400	5.2	0.75
OT	800	10.5	1.55
OT	1,600	20.90	2.51
IV	1,140	15.0	33.6

iv. Estimated "worst case" Data (based on Cmax of 2.51 ng/mL/1600µg):

OT	Units)	104.5	12.55
OT	Units)	229.9	27.61

v. Fentanyl intravenous dose of 15 µg/kg produced mean Cmax of 33.6 ng/ml. OT dose of 229.9 µg/kg is required to yield an estimated Cmax of approximately same magnitude, 27.61 ng/ml.

iv. Study assumes motivations for taking drug are identical. The 15 µg/kg iv dose, being large and slowly administered, was administered over 6 to 8 minutes. Drug abusers may inject drugs rapidly, which could result in a higher Cmax with short-acting

drugs (e.g. fentanyl); therefore, this could be an underestimation of the attainable iv fentanyl dose.

v. The 15 µg/kg is probably a large dose relative to that required to produce the subjective euphoric effects associated with abuse liability of fentanyl products. Human lab studies indicated that iv fentanyl doses of only 0.7-1.8 µg/kg (which are 4.7%-12% of the 15 µg/kg dose for which Cmax data is available) are sufficient to produce such subjective effects (Zachny *et al.*; Greenwald *et al.*). The C_{max} is considerably greater than what would produce a positive subjective response.

3. References cited:

1. Gorodetzsky, CW and Martin WR. "A comparison of fentanyl, droperidol, and morphine," Clin Pharm. & therap., 1965, 6:731-9.

2. Zacny, JP, Lichtor, JL, Zaragoza JG, deWit H, "Subjective and behavioral responses to intravenous fentanyl in healthy volunteers," Psychopharmacology, 1992, 107:319-326.

3. Greenwald MK, June HL, Stitzer ML, Marco AP, "Comparative clinical pharmacology of short-acting mu opioids in drug abusers," J. Pharm. Exper. Therap., 1996, 277:1228-36.

4. Shafer SL, Varvel JR, "Pharmacokinetics, pharmacodynamics and rational opioid selection, Anesthesiology, 1991: 74: 53-63.

5. Draft Guidelines for Abuse Liability Assessment, Subcommittee on Guidelines for Abuse Liability Assessment, DAAC, FDA, US PHS, 1992.

6. Porter J, Jick H., "Addiction rare in patients treated with narcotics," New Engl. of Med., 1980, 302: 123.

7. Yaster, M., Maxwell, LG, "Opioid agonists and antagonists," In: Schechter N., Berde C.B., Yater M., Eds., Pain in infants and children," Baltimore: Williams & Wilkins, 1993: 147.

4. Conclusions:

The CSA Schedule II narcotic provisions will address most of the abuse and diversion concerns with approval of Actiq. Placement of the product in CII will impose the strictest possible regulations allowable for any controlled substance.

a. The sponsor maintains that from the drug abusers' perspective, the OTFC provides a relatively inefficient route to administer fentanyl. Cmax levels were compared by the injectable vs. OTFC formulations. Lower Cmax levels may be sufficient for attaining the sought-after subjective response, and not require doses 15 times as large to achieve comparable blood levels Issues related to dependence liability assessment, addicts who desire to maintain an addiction and the perspective of the non-drug abusing population were not considered for this particular product, although there is considerable data relative to those issues in the public domain.

b. If multiple OTFC units are used simultaneously high fentanyl blood levels can be achieved; these are comparable to those resulting

following anesthetic intravenous doses.

c. Such high blood levels are probably not needed to achieve subjective euphoric effects; subjective effects associated with abuse liability might be achievable in non-tolerant individuals with as few as one or two OTFC doage units (altho slower).

d. Disposal of Incompletely-Used OTFC Dosage Units. Methods should be recommended for disposal in the product label. Once administered to the patient, the product falls outside the regulatory framework of the Controlled Substances Act and its applicable provisions. Hospitals, clinics, hospices, etc., need to establish their own internal procedures for inventorying these unused or partially used products, accounting for them and disposing of them.

Therefore, the product should be labeled as recommended by the Sponsor:

(1) As a CII narcotic.

(2) In addition, the relative merits of restricted use of the drug to the hospital, hospice and/or clinical setting to be administered directly by a health care provider only, as opposed to home use, should be considered. If available at retail level, patient information should include directions on disposal of the product.

(3) Hospitals, clinics and hospices should be advised to be vigilant relative to distribution of the product within the hospital setting. As considerable amounts of active drug are still present after use by the patient, the hospitals, clinics and hospices should be advised to ensure that unused or partially used products are inventoried, destroyed, and not diverted for subsequent sale or redistribution for abuse purposes.

(4) The Sponsor should consider a child resistant container for the product.

/s/ 7/26/97

Michael Klein, Ph.D.
HFD-170 July 26, 1997

CC:
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