

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20747**

**PHARMACOLOGY REVIEW(S)**

**Review and Evaluation of Pharmacology and Toxicology  
Division of Anesthetic, Critical Care & Addiction Drug Products  
HFD-170/Kathleen Haberny**

**NDA 20-747 Amendment No. 049 / September 4, 1998 / Revised Draft Labeling**

**Review Completion Date: September 24, 1998**

**Information to sponsor Yes ( ) No (x)**

**Sponsor: Anesta Corp., 4745 Wiley Post Way Suite 650, Salt Lake City, Utah 84116**

**Drug Name: Actiq® (oral transmucosal fentanyl sitrate, OTFC®)**

**CONCLUSIONS**

The revised draft labeling sections relevant to Carcinogenesis, Mutagenesis, and Impairment of Fertility, and Pregnancy under Precautions, submitted for review on September 4, 1998, are acceptable.

*ISI*

*9/24/98*

Kathleen A. Haberny, Ph.D.

*ISI*

*9/24/98*

Team Leader: Don H. Jean, Ph.D.

cc: NDA 20-747 Arch  
HFD 170/Division File  
HFD 170 /K Nolan  
HFD 170/ K Haberny

MAY 12 1998

1

Pharmacology/Toxicology Review and Evaluation of NDA Action Letter Response  
Division of Anesthetic, Critical Care & Addiction Drug Products  
HFD-170/Kathleen Haberny

NDA: 20-747

April 30, 1998 / Amendment No. 037: Response to not approvable action letter.

Information to sponsor Yes (✓) No ( )

Completion Date: May 8, 1998

Sponsor: Anesta Corporation  
4745 Wiley Post Way, Suite 650  
Salt Lake City, UT 84116

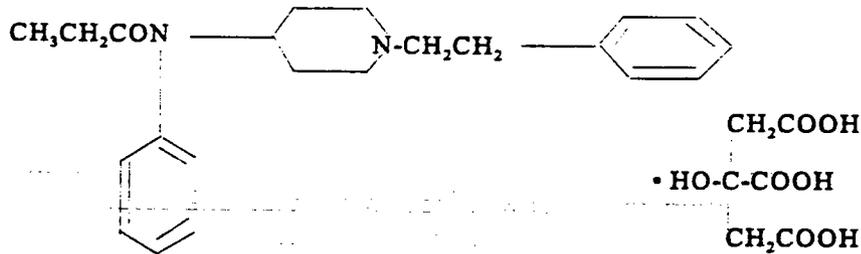
Manufacturer: Fentanyl citrate:

Drug Product: Abbott Laboratories, Hospital Products Division, 1401 N.  
Sheridan Rd., North Chicago, IL 60064-4000

Drug Name: Actiq™ (Oral Transmucosal Fentanyl Citrate)

Chemical Name: N (1-Phenethyl-piperidyl) propionanilide citrate

Structure:



Molecular Weight: 336.5 (free base), 528.58 (citrate salt)

Relevant INDs/NDAs/DMFs:

DMF   
DMF  
DMF  
IND

Abbott Laboratories, North Chicago, IL

NDA 20-195 Fentanyl Oralet® (Oral Transmucosal Fentanyl Citrate)  
100, 200, 300, and 400 µg fentanyl base

**Drug Class:** Synthetic phenyl piperidine derivative, opioid analgesic

**Indication:** Management of chronic pain, particularly breakthrough pain, in opioid tolerant patients

**Clinical Formulation (and components):** Solid lozenge on a plastic stick, containing fentanyl base (200, 400, 600, 800, 1200, or 1600  $\mu\text{g}/\text{unit}$ ) and per each 90,000 units (theoretical 268.8 kg batch weight): sucrose ( ) kg), corn syrup solids (corn syrup, D.E. 43, ( ) kg), artificial raspberry flavor ( ( ) g) and white dispersion G.B. dye ( ( ) g), or approximately per unit: 1.35 gm sucrose, ( ) gm corn syrup ( ) gm artificial raspberry flavor, and ( ) gm white dispersion G.B. dye.

**Route of Administration:** Oral/Transmucosal

**Preclinical Studies:** No new studies submitted.

#### LABELING REVIEW

The proposed package insert sections relevant to Carcinogenesis, Mutagenesis, and Impairment of Fertility, and Pregnancy under Precautions, are copied as follows:

#### RECOMMENDATIONS

No new animal studies were submitted in this amendment, and there are no new preclinical issues. This NDA is approvable from a pharmacology and toxicology perspective.

**To Sponsor:** The proposed label is acceptable with minor revisions, described below.

The proposed pregnancy section is acceptable.

**Draft of pharmacology portion of letter to sponsor:**

Copy under recommendations.

*/S/* *5/8/98*  
\_\_\_\_\_  
Kathleen A. Haberny, Ph.D.  
*/S/* *5/12/98*  
\_\_\_\_\_  
Team Leader: Dou H. Jean, Ph.D.

cc: IND Arch  
HFD 170/Division File  
HFD 170 /K Nolan  
HFD 170/ K Haberny

Review and Evaluation of Pharmacology/Toxicology  
Division of Anesthetic, Critical Care & Addiction Drug Products  
HFD-170/Kathleen Haberny

NDA: 20-747

November 11, 1996/Original Application

Information to sponsor Yes (✓) No ( )

Completion Date: April 23, 1997

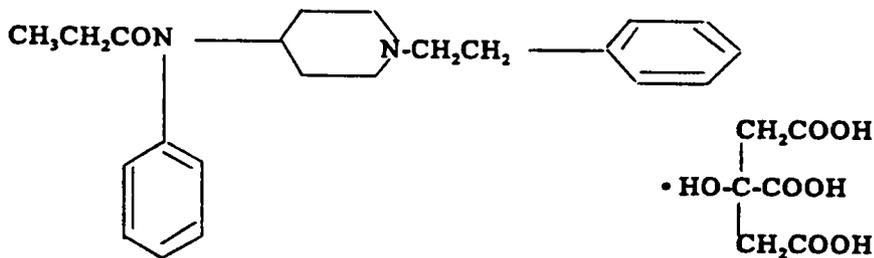
Sponsor: Anesta Corporation  
4745 Wiley Post Way, Suite 650  
Salt Lake City, UT 84116

Manufacturer: Fentanyl citrate: Johnson Matthey, Inc., 2002 Nolte Drive, West Deptford,  
NJ 08066  
Drug Product: Abbott Laboratories, Hospital Products Division, 1401 N.  
Sheridan Rd., North Chicago, IL 60064-4000

Drug Name: Actiq™ (Oral Transmucosal Fentanyl Citrate)

Chemical Name: N (1-Phenethyl-piperidyl) propionanilide citrate

Structure:



Molecular Weight: 336.5 (free base), 528.58 (citrate salt)

Relevant INDs/NDAs/DMFs:

DMF

DMF

DMF

IND

NDA 20-195 Fentanyl Oralet® (Oral Transmucosal Fentanyl Citrate) Anesta Corp.  
100, 200, 300, and 400 µg fentanyl base

Abbott Laboratories, North Chicago, IL  
Anesta Corp.

Drug Class: Synthetic phenyl piperidine derivative, opioid analgesic

**Indication:** Management of chronic pain, particularly breakthrough pain, in opioid tolerant patients

**Clinical Formulation (and components):** Solid lozenge on a plastic stick, containing fentanyl base (200, 400, 600, 800, 1200, or 1600 µg/unit) and per each 90,000 units (theoretical kg batch weight): sucrose (            kg), corn syrup solids (corn syrup, D.E. 43, kg), artificial raspberry flavor            g) and white dispersion G.B. dye            g) or approximately per unit:            gm sucrose,            gm corn syrup,            gm artificial raspberry flavor, and            gm white dispersion G.B. dye.

**Proposed Clinical Dose:** Initial dose 200 mcg; Effective dose following initial titration 200, 400, 600, 800, 1200, or 1600 mcg (mean 789 mcg) per episode of breakthrough pain; Maximum consumption after appropriate dose achieved, no more than 4 units/day (6400 mcg/day).

**Route of Administration:** Oral Transmucosal

**Studies Reviewed within this Submission:**

**Mutagenicity Studies:**

Bacterial Reverse Mutation Assay, Report # RA/FC/96/002  
In Vitro Mammalian Cell Gene Mutation Test, Report #RA/FC/96/001  
Micronucleus Cytogenetic Assay in Mice, Report #RA/FC/96/003

**Metabolism Studies:**

Human Fentanyl Biotransformation: Identification of Responsible Cytochrome P450 Isoforms, Report #CR/FC/96/001

All other information in this review is based on a summary of published literature reports on fentanyl citrate, previously reviewed studies submitted under NDA 20-195 (Fentanyl Oralet®) and studies for this submission conducted under IND

*Note: Portions of this review were excerpted directly from the sponsor's submission.*

## TABLE OF CONTENTS

A. INTRODUCTION/DRUG HISTORY

Page #

3

	<u>Page #</u>
<b>B. PHARMACOLOGY</b>	<b>4</b>
Efficacy	4
Mechanisms of Action	4
Secondary Pharmacological Activities	5
Tolerance	5
Dependence	5
Abuse Liability	6
Drug Interactions	6
<b>C. SAFETY PHARMACOLOGY</b>	<b>7</b>
Effects on the Cardiovascular System	7
Effects on the Cerebrovascular System	8
Effects on the Respiratory System	8
Effects on the Hepatic System	8
Effects on the Renal System	9
Effects on the Endocrine System	9
<b>D. PHARMACOKINETICS</b>	<b>9</b>
ADME	9
Absorption	9
Distribution	10
Metabolism	10
Excretion	12
<b>E. TOXICOLOGY</b>	<b>13</b>
Single Dose Toxicology	13
Repeat Dose Toxicology	13
Carcinogenicity	13
Reproductive Toxicology	13
Genotoxicology	14
Special Toxicology Studies	18
<b>F. LABELING REVIEW</b>	<b>18</b>
<b>G. OVERALL SUMMARY AND DISCUSSION</b>	<b>20</b>
<b>H. CONCLUSIONS</b>	<b>25</b>
<b>I. RECOMMENDATIONS</b>	<b>27</b>

### INTRODUCTION/DRUG HISTORY

Fentanyl citrate, a synthetic phenyl piperidine derivative, is a  $\mu$ -opioid receptor agonist with analgesic potency approximately 80-100 times that of morphine. Fentanyl has been marketed in several dosage forms for nearly 29 years, producing a long record of safety and efficacy in the treatment of pain. Fentanyl citrate is currently available for intravenous and intramuscular injection (Sublimaze<sup>®</sup>, NDA 16-619), transdermal delivery (Duragesic<sup>®</sup> fentanyl transdermal system, NDA 19-813) and oral transmucosal delivery (Oralet<sup>®</sup>, Oral Transmucosal Fentanyl Citrate, NDA 20-195).

Fentanyl Oralet® (200, 300, 400, 500, 600 and 800 µg/unit) was approved in 1993 (NDA 20-195) for presurgical anesthetic medication and for conscious sedation prior to diagnostic and therapeutic procedures in children and adults. Actiq™ (Oral Transmucosal Fentanyl Citrate) was designed for delivery of fentanyl citrate in six strengths (200, 400, 600, 800, 1220 and 1600 µg/unit) as a supplemental analgesic dose during episodes of breakthrough pain during chronic opioid therapy in opioid-tolerant cancer patients. Oralet® and Actiq™ are formulated as solid, flavored lozenges on plastic handles (lollipop), to be sucked for approximately 15 minutes for drug release. Oral transmucosal fentanyl delivery has several advantages; rapid onset and short duration of analgesic effect, convenient non-invasive delivery, titratability and the minimalization of the use of high maintenance opioid doses that can increase the incidence of adverse events and side effects. Actiq™ per se has not been previously marketed in any country.

---

## PHARMACOLOGY

### Efficacy

The sponsor reported no preclinical data supporting the efficacy of oral transmucosal fentanyl citrate, because no suitable animal model for this route of administration has been developed. The analgesic efficacy of fentanyl citrate by other routes in animals is well established and widely reported in the literature.

Fentanyl analgesia, associated with decreased somatic and cardiovascular responses to pain, has been demonstrated in numerous preclinical studies, with considerable variability in the resulting ED<sub>50</sub>s and effective plasma concentrations across species. The median effective subcutaneous (SC) fentanyl doses in the mouse acetic acid-induced writhing test, tail immersion test, phenylquinone writhing test, formalin-induced hind paw pain test, and tail-clamp test, were 11.5, 94, 34, 50 and 80 mcg/kg respectively. In the tail-clamp test, the onset of fentanyl analgesia was approximately 4 minutes, peak analgesic effect occurred at 10-15 minutes and duration of action was approximately 30 minutes. In the rat, the fentanyl ED<sub>50</sub>s in the tail pressure and anti-bradykinin tests were 20 and 8 mcg/kg SC respectively. Intravenous (IV) fentanyl (ED<sub>50</sub> 11.35 mcg/kg) antagonized the response to tooth pulp stimulation in rabbits for approximately 26 minutes.

Maximal analgesia was achieved in dogs at a plasma fentanyl concentration of approximately 30 ng/ml, and in Rhesus monkeys at 43.4 ng/ml. The effective anesthetic doses ranged from 70-3000 µg/kg and plasma concentrations from 30-400 ng/ml in the dogs. In the monkeys, significant respiratory and analgesic effects were observed at plasma fentanyl concentrations as low as 3 ng/ml.

### Mechanisms of Action

The pharmacological effects of fentanyl are mediated primarily via agonist activity at the µ1- (high affinity) and µ2- (low affinity) opioid receptors. Fentanyl binding in the central

nervous system (CNS) occurs in the following sites in sequentially decreasing order: midbrain and striatum, hypothalamus, cerebral cortex, hippocampus, brainstem, spinal cord, and cerebellum. Fentanyl interacts to a lesser extent with central and peripheral (e.g. vascular)  $\alpha$ -adrenergic and muscarinic ( $M_3$  subtype) receptors.

### Secondary Pharmacological Activities

Secondary effects of fentanyl in mice and dogs are typical of those induced by  $\mu$ -opioid drug administration, and are reversible by the  $\mu$ -opioid antagonist nalorphine. These effects included dose-related increases in spontaneous motor activity and response to touch, circling, Straub tail reaction, increased muscle tone and mydriasis in mice (at 10-1000  $\mu\text{g}/\text{kg}$  SC), and decreased motor activity, ataxia, depressed responsiveness to auditory and painful stimuli, bradycardia, respiratory depression, salivation and defecation in dogs (at 12.5-1000  $\mu\text{g}/\text{kg}$  IM). In humans, common fentanyl side effects are respiratory depression, hypotension, bradycardia, muscle and chest wall rigidity, pruritus, nausea and vomiting.

### Tolerance

A decrease in analgesia with repeated administration was demonstrated using the hot water tail-flick test in rats administered fentanyl (40  $\mu\text{g}/\text{kg}$  IP, once every two days) for ten days. In that study, the tail-flick response was not different in treated and control animals at ten days, and the reduction of response persisted for up to fourteen days after fentanyl administration was terminated. In rats made tolerant to fentanyl by continual infusion with fentanyl (0.01 mg/kg/h for 1 week), cross tolerance was demonstrated in a tail-flick procedure for buprenorphine, but not for morphine, etorphine, methadone, meperidine, and levorphanol analgesia. Intermittent opioid administration produced less tolerance to the analgesic effects than did continuous infusion in mice, and painful stimuli may further decrease the development of fentanyl tolerance. Rats exposed to mechanical pain during four days treatment with fentanyl exhibited analgesic responses similar to those of rats that received saline for four days, upon challenge with fentanyl on day five. Rapid and extensive tolerance to fentanyl side effects was also demonstrated in preclinical studies. For example, dogs administered four doses of fentanyl thirty minutes apart, exhibited hypotension following the first dose, but little or no additional hypotensive effect after the subsequent doses.

### Dependence

Fentanyl dependence has been demonstrated in guinea pigs and dogs. Withdrawal contractures were induced by exposure to naloxone in ileal longitudinal muscle with attached myenteric plexus isolated from guinea pigs made tolerant to fentanyl. In dogs, increasing doses of fentanyl (1.5-100  $\mu\text{g}/\text{kg}$  IV, every 20 min for 200 min) resulted in increased arterial blood pressure responses to somatic nerve stimulation at 90 minutes after drug withdrawal.

**Abuse Liability**

There were no literature reports of fentanyl abuse liability studies in animals. However, it has been demonstrated that laboratory animals will self-administer morphine and other  $\mu$ -opioid agonists, and fentanyl abuse in humans has been reported.

**Drug Interactions**

Selected examples from literature reports of drug interactions with fentanyl in animals are presented below. For references, see NDA 20-747, Vol. 9/54, pp. 5-19 through 5-129.

Species	Fentanyl Dose	Coadministered Drug	Test	Results
<i>Additive/Synergistic Interactions</i>				
Rat	15 $\mu$ g/kg SC	Calcium channel blockers clonidine (100 $\mu$ g/kg SC) and verapamil (10 $\mu$ g/kg SC)	Tail flick, hot plate tests	Synergistic increase in analgesia
Rat	Variable with dexmedetomidine, 300 $\mu$ g/kg IP with other drugs	A. $\alpha$ 2-adrenergic agonists dexmedetomidine (variable) or medetomidine (200, 300 $\mu$ g/kg IP) B. $\alpha$ 2-adrenergic antagonist atipamezole (1 mg/kg IP) + $\mu$ -opioid antagonist nalbuphine (2 mg/kg IP) or $\kappa$ -agonist butorphanol (0.4 mg/kg IP)	A. Righting reflex, Isobolographic analysis B. Righting reflex, Isobolographic analysis,	A. Synergistic potentiation B. Reversal of potentiation in 'A' above
Rat	20 $\mu$ g/kg SC	A. N-type calcium channel blocker KB-2796 (1, 5, 15 mg/kg SC) B. L-type calcium channel agonist Bay K 8644 (0.25, 0.5, 1 mg/kg SC)	A. Tail flick B. Tail flick	A. Potentiation B. No effect
Rabbit	15 $\mu$ g/kg IV	Midazolam (700 $\mu$ g/kg IV)	Antinociception, respiratory depression	Enhanced antinociception, no increase in respiratory depression
Rabbit	ED50, 2xED50, ED90 IV	Tricyclic antidepressant imipramine (1, 2.1, 3.2 mg/kg IV)	Antinociception (tooth pulp stimulation)	Supra-additive effect, no increase in PaCO <sub>2</sub>
Dog	IV loading dose followed by constant infusion at 0.02, 0.05 mcg/kg/min	Midazolam (loading dose and infusion 2.4, 9.6, 28.8 $\mu$ g/kg/min)	Enflurane MAC reduction	MAC reduction
Cat	IV	Non-depolarizing neuromuscular blocking agent: vecuronium derivative ORG 9426	Muscle relaxing effects, time course, recovery time	No effects
Lambs (newborn)	3 mg/kg IV	Pentobarbital (4 mg/kg IV)	Analgesia, peripheral & central hemodynamic effects	Potentiation of all effects
Sheep	5 $\mu$ g/kg IV	(Dopaminergic) neuroleptic drugs droperidol (5 $\mu$ g/kg IV) or zuclopenthixol (100 $\mu$ g/kg IV)	Nociceptive threshold	Potentiation

Species	Fentanyl Dose	Coadministered Drug	Test	Results
<b>PK Interactions</b>				
Rats & Rabbits	Variable	Liposomal (phosphatidylcholine and cholesterol) carriers	Thermomodulation, analgesia	Potentiation
<b>Antagonists</b>				
Rat (male Sprague-Dawley)	100 µg/kg IV	A. Prazosin (α1-adrenergic blocker, 50, 250 µg/kg IV) B. Yohimbine (α2-adrenergic blocker, 1.15, 2.3 mg/kg IV)	Antagonism of muscular rigidity	A. Antagonized fentanyl-induced rigidity B. Potentiated fentanyl rigidity
Rat	25, 100 µg/kg IV	3-hydroxymethyl-8-carboline (3-HMC, benzodiazepine antagonist, 10 mg/kg IV)	Antagonism of fentanyl induced cerebral metabolic & respiratory depression, analgesia	Enhanced analgesia, antagonized hypnotic, respiratory depressant, cardiovascular effects
Dog	40 µg/kg IV	Atropine (antimuscarinic agent, 0.1 mg/kg IV)	Antagonism of fentanyl induced blood pressure, bradycardia	Antagonized bradycardia, no effect on blood pressure
Dog	0.4 mg/kg IM	Naloxone (0.01, 0.1, 1.0, 10 mg/kg IV) Doxapram (5 mg/kg IV)	Reversal of fentanyl-droperidol-pentobarbital anesthesia	Naloxone & doxapram antagonized anesthesia better than naloxone alone
Dog	50 µg/kg IV	Naloxone (0.4 mg IV)	Hemodynamic effects	Reversal of decr in MAP, heart rate, plasma norepinephrine & epinephrine, less so with induced hypocapnia

## SAFETY PHARMACOLOGY

### Effects on the Cardiovascular System

Fentanyl had no effects in tests of coronary circulation and myocardial metabolism, demonstrated in isolated canine coronary rings with and without endothelium (resting or precontracted at 100 ng/ml), isolated rat hearts (100 ng/ml) and intact pigs (300 µg/kg

IV). Low (2.5-3  $\mu\text{g}/\text{kg}$ ) but not high (30-160  $\mu\text{g}/\text{kg}$ ) fentanyl doses increased the left ventricular dP/dt in anesthetized dogs. Fentanyl decreased heart rate in isolated rabbit hearts (5-80 ng/ml), and decreased heart rate (5-100  $\mu\text{g}/\text{kg}$  IV) and blood pressure in intact dogs, with a plateau effect from 70  $\mu\text{g}/\text{kg}$  (plasma concentration 30 ng/ml). In another study in dogs fentanyl (50  $\mu\text{g}/\text{kg}$  IV) reduced heart rate, mean arterial blood pressure, coronary blood flow and myocardial oxygen consumption, but had no effect on atrial filling pressures, left ventricular end-diastolic pressure, cardiac output, stroke volume, left ventricular dP/dt and total body oxygen consumption. In neonatal lambs, fentanyl (up to 4.4 mg/kg IV) induced respiratory depression, increased arterial carbon dioxide tension decreased arterial oxygen tension, and decreased renal blood flow, without significant effects on cardiac output, heart rate, mean arterial blood pressure, and blood flow to the stomach, large and small intestines, muscles and skin.

#### Effects on the Cerebrovascular System

Fentanyl (up to 100  $\mu\text{g}/\text{kg}$  IV) decreased cerebral blood flow (35%) and cerebral oxygen metabolism (50%), but higher doses (up to 400  $\mu\text{g}/\text{kg}$ ) had no further effects on these parameters in rats. In anesthetized dogs, fentanyl (25-100  $\mu\text{g}/\text{kg}$  IV) had no effects on hypoxia- or hypercapnia-induced alterations in cerebral vascular responsiveness and blood flow. Fentanyl (cumulative dose 4.4 mg/kg IV) had no effect on cerebral blood flow, oxygen delivery and oxygen consumption in mechanically ventilated neonatal lambs, although there were regional, naloxone reversible decreases in blood flow to the spinal cord, cerebellum, medulla, diencephalon and subcortical white matter.

#### Effects on the Respiratory System

Intravenous fentanyl (11.5  $\mu\text{g}/\text{kg}$ ) induced respiratory depression in rabbits, measured by an increase (74%) in  $\text{PaCO}_2$ . In dogs, fentanyl (10-40  $\mu\text{g}/\text{kg}$  IV) dose-dependently decreased respiratory minute volume (up to 98%) as a result of decreased respiratory rate and tidal volume, with maximum effects at one minute and marked recovery over five minutes. In another study, administration of 10  $\mu\text{g}/\text{kg}$  IV fentanyl in dogs also resulted in an increase in end-tidal  $\text{CO}_2$  from 43 to 70 torr over 10 minutes, and complete recovery at 180 minutes. Fentanyl-induced changes in respiration in dogs were reversed with controlled/assisted ventilation and with naloxone administration.

#### Effects on the Hepatic System

No hepatotoxicity, measured by ASAT, ALAT, LDH levels, cell viability, intracellular ATP, and  $^{14}\text{C}$ -valine incorporation into proteins, was observed in isolated rat hepatocytes exposed to fentanyl (74.3 and 148.6 nM). Fentanyl (15.6  $\mu\text{g}/\text{kg}$  IP, q.d.) administered for six days, increased the liver enzyme serum glutamic pyruvic transaminase (SGPT) but had no effect on serum glutamic oxaloacetic transaminase (SGOT) and was not associated with liver necrosis in rats. Fentanyl (350  $\mu\text{g}/\text{kg}$ ) administered over 3 hours, slightly increased SGOT and AGPT in cirrhotic and noncirrhotic rats, but resulted in no increase in hepatocellular damage in either group.

### Effects on the Renal System

Fentanyl (25  $\mu\text{g}/\text{kg}$  IV) infusions in anesthetized dogs over 10 minutes, decreased urine volume, glomerular filtration rate and renal plasma flow, and increased renal vascular resistance, lasting 30-90 minutes post drug administration. In another study in dogs, fentanyl (0.1-1.0 mg/kg) decreased urine output and free water clearance, and increased urine osmolarity.

### Effects on the Endocrine System

Fentanyl (10  $\mu\text{g}/\text{kg}$  IV) increased growth hormone secretion in male rats in a bell-shape dose-response pattern. This effect was antagonized by administration of the  $\mu$  and  $\kappa$  opioid receptor antagonist MR-2266 (6 mg/kg IV) and the  $\mu$  opioid receptor antagonist bremazocine (0.1 mg/kg IV), suggesting a role of  $\mu$  opioid receptors in fentanyl-induced growth hormone secretion. In cardiomyocytes isolated from neonatal rats, fentanyl (10-50 ng/ml) increased the release of atrial natriuretic peptide and the effect was antagonized by naloxone. Additional effects of fentanyl exposure that were not antagonized by naloxone in these cells were growth/development of myocyte contractile elements, increased protein biosynthesis and an increase in spontaneous beating rate.

## PHARMACOKINETICS

A study in 6 mongrel dogs administered fentanyl intravenously, or to the buccal mucosa (solution pH 6.6, 7.2, or 7.7) followed by clamping of the drug delivery cell for 60 minutes, demonstrated increased  $C_{\text{max}}$ , bioavailability and permeability coefficient by 3x (pH 7.2) to 5x (pH 7.7) with increasing basicity of the buccal fentanyl solution. The terminal elimination half life was similar after intravenous ( $244 \pm 68$  min) and buccal (pH 7.7:  $205 \pm 89$  min, pH 7.2:  $205 \pm 65$  min, and pH 6.6:  $196 \pm 48$  min) administration. The  $T_{\text{max}}$  for all buccal solutions was within 10 minutes of system removal.

In healthy, male human volunteers, a single dose of transmucosal fentanyl (OTFC) (15  $\mu\text{g}/\text{kg}$  over 15 minutes) resulted in a  $T_{\text{max}}$  of 23 minutes (range            minutes),  $C_{\text{max}}$  of 2.7 ng/ml (range            ng/ml), half-life of 6.6 hours (range            hours), total plasma clearance of 0.5 L/hr/kg (range            L/hr/kg), total body clearance of approximately 13.3 ml/kg/min, and bioavailability of 50% (range            %). The volume of distribution was 3-6 L/kg and terminal elimination half-life 219 minutes in opioid non-tolerant adults. The onset of action was approximately 5 minutes (range            minutes).

## ADME

### Absorption

In mongrel dogs, administered buccal fentanyl in a pH-buffered solution cell for 60 minutes, fentanyl was detected in plasma at 6 minutes, and the  $T_{\text{max}}$  was 10 minutes after drug administration ceased. Buccal fentanyl absorption, bioavailability and permeability in dogs

increased (3x to 5x) with increasing fentanyl solution pH (from pH 6.6 to 7.7). Bioavailability ranged from approximately 20% (pH 6.6) to 57% (pH 7.7). In another study in dogs, all fentanyl that was removed from the buccal solution was absorbed into the systemic circulation with no depot effect, adsorption or buccal mucosa metabolism of the drug.

In humans, the bioavailability of oral transmucosal fentanyl citrate is approximately 50%, resulting from absorption of 25% of the total dose from the buccal mucosa and absorption of approximately 1/3 of the remaining 75% total dose that is swallowed (25% of the total dose). Approximately 67% of the swallowed fentanyl (50% of the total dose) undergoes hepatic and duodenal first-pass metabolism.

### Distribution

In a study in rats, intravenously administered fentanyl was detected in brain, heart, and lung at equivalent concentrations with plasma fentanyl at 1.5 minutes, and in muscle and fat at equivalent concentrations at 120 minutes after intravenous administration. Additionally, fentanyl was measured in liver, gastric contents, small intestine, and kidneys. Muscle and brain affinities for fentanyl were 4:1 and 5:1 respectively, and affinity of fat for fentanyl was approximately 35:1. The high affinity of fat for fentanyl suggested that fentanyl could accumulate with repeated administration, and be reintroduced into circulation over time. Fentanyl crossed the placenta in rabbits and sheep with resulting ratios of fetal to maternal plasma fentanyl levels of 0.3 in both species.

The metabolites phenylacetic acid and norfentanyl, and minor metabolites including the pharmacologically active p-hydroxy (phenethyl) fentanyl, were detected in gastric contents, brain, heart, lung, liver, kidney, muscle and fat in rats.

Fentanyl plasma protein binding is variable among species, representing approximately 60%-80% of unchanged drug in rabbits and dogs. Plasma protein binding is reported in humans to be approximately 80%, predominantly to  $\alpha$ -1-acid glycoprotein.

Fentanyl is rapidly distributed after intravenous administration in humans to the brain, lung, kidney, spleen and heart. The concentration-time curve in humans is best described by a three-compartment model, with a rapid distribution phase half-life of approximately 1.7 minutes, slow distribution phase half-life of 13 minutes, and terminal elimination half-life of 219 minutes.

Fentanyl crossed the human placenta resulting in a fetal:maternal plasma level ratio of 0.8.

### Metabolism

In rats, 25% of radiolabel was detected as metabolites at 15 minutes and 80% as metabolites at 4 hours after administration of  $^3\text{H}$ -fentanyl.

Fentanyl was metabolized in the microsomal fraction of mouse liver homogenates to norfentanyl, phenylacetic acid, and four minor metabolites including p-hydroxy (phenethyl)

fentanyl. Fentanyl metabolism also occurred in mouse kidney and adrenal gland. The major metabolic pathway for fentanyl in rats is hepatic oxidative N-dealkylation to norfentanyl and phenylacetic acid, and small amounts of pharmacologically active p-hydroxy-(phenethyl)fentanyl. Minor pathways in rats include amide hydrolysis, hydroxylation and conjugation. Fentanyl metabolism occurs to a minor degree in rat kidney.

In humans, fentanyl undergoes extensive and rapid metabolism. In one study, more than 80% of an intravenous dose of fentanyl was recovered as metabolites (76% in urine and 8% in feces). Metabolites were detected in plasma within two minutes of drug administration, and exceeded parent drug after 30 minutes. The identities of the fentanyl metabolites were determined in the following study.

**Report #CR/FC/96/001: Human Fentanyl Biotransformation: Identification of Responsible Cytochrome P450 Isoforms**

This study was designed to identify the metabolites of fentanyl citrate in humans, to determine the roles of human liver and duodenal microsomal fentanyl metabolism and to identify the cytochrome P450 enzyme isoforms involved in human fentanyl metabolism. Earlier clinical investigations found norfentanyl [4-N-(N-propionylanilino)piperidine] and despropionylfentanyl [1-(2-phenylethyl)-4-N-analinopiperidine] in plasma and norfentanyl [4-N-(N-propionylanilino)piperidine], hydroxyfentanyl [1-(2-phenylethyl)-4-N-(hydroxypropionylanilino)piperidine], and hydroxynorfentanyl [4-N-(N-hydroxypropionylanilino)-piperidine] in urine after fentanyl administration.

**Methods:** Microsomes prepared from human (organ donor) duodenum (0.1-0.2 mg/ml) and liver (50 µg/ml) were incubated with fentanyl (10 µM) for 7 minutes at 37°C (concentration 0.25 mg/ml, incubation time 30 for cDNA-expressed P450 experiments). Metabolites were extracted and identified using

The rate of norfentanyl formation was measured in microsomes from hepatocytes with cDNA-expressed P450 isoforms, to determine which isoforms were involved in the metabolic pathway.

Using another method to determine P450 isoform participation in fentanyl metabolism in humans, the following inhibitors were introduced to duodenal and hepatic microsome preparations.

	p450 Isoform Inhibited	Inhibitor Type	Final Concentration
Furaphylline	1A2	Mechanism-based inhibitor	20 µM
Coumarin	2A6	Competitive inhibitor	100 µM
Orphenadrine	2B6	Mechanism-based inhibitor	50 µM

	p450 Isoform Inhibited	Inhibitor Type	Final Concentration
Furaphylline	1A2	Mechanism-based inhibitor	20 $\mu\text{M}$
Sulphaphenazole	2C9	Competitive inhibitor	50 $\mu\text{M}$
Quinidine	2D6	Competitive inhibitor	5 $\mu\text{M}$
Diethyldithiocarbamate	2E1/2A6	Mechanism-based inhibitor	100 $\mu\text{M}$
4-methylpyrazole	2E1	Competitive inhibitor	500 $\mu\text{M}$
Troleandomycin	3A4	Mechanism-based inhibitor	100 $\mu\text{M}$
Midazolam	3A4	Competitive inhibitor	100 $\mu\text{M}$

**Results:** In liver microsomes, the major metabolite detected using \_\_\_\_\_ was norfentanyl (1440 pmol/min/mg) representing 99% of all metabolites, followed by despropionylfentanyl (1.1 pmol/min/mg) and hydroxyfentanyl (0.58 pmol/min/mg). Hydroxynorfentanyl was detected after 90 minutes, but not after 7 minutes incubation of microsomes with fentanyl. In human duodenal microsomes, norfentanyl (0.01-0.41 nmol/min/mg) was the detected after incubation with fentanyl.

In the microsomes containing cDNA-expressed cytochrome P450 isoforms, those containing P450 3A4 had the highest rate of norfentanyl formation, at 61 pmol/min/mg protein. Further, addition of troleandomycin and midazolam decreased formation of norfentanyl 63% and 99% respectively in liver microsomes, indicating that the P450 3A4 isoform was the major enzyme responsible for the transformation. In duodenal microsomes, troleandomycin and midazolam inhibited norfentanyl formation 55%-78% and 35%-56% respectively. Norfentanyl formation was inhibited by diethyldithiocarbamate but not by coumarin and 4-methylpyrazole. No other inhibitor decreased norfentanyl formation.

**Conclusions:** The results of this study indicate that fentanyl citrate is primarily metabolized to norfentanyl in the human liver and duodenum. Minor hepatic metabolites of fentanyl are despropionylfentanyl, hydroxyfentanyl and hydroxynorfentanyl. The P450 3A4 isoform is the major enzyme responsible for fentanyl metabolism in humans.

### Excretion

Fentanyl is excreted predominantly as metabolites in urine and to a lesser extent in feces. For example, after intravenous administration in dogs, 32% [ $^3\text{H}$ ]-fentanyl was excreted in urine, with 4%-6% excreted as unchanged fentanyl, during the first 6 hours. After intravenous fentanyl administration in humans, less than 8% of the total dose is eliminated unchanged (6% in urine and 1% in feces). Approximately 75% intravenous dose is excreted in urine and 9% in feces as metabolites.

---

## TOXICOLOGY

### Single Dose Toxicology

The sponsor reported no preclinical data supporting the safety of oral transmucosal fentanyl citrate because a suitable animal model for this route of administration has not been developed. The profile of acute fentanyl toxicity by other routes in animals is well established.

The median lethal fentanyl doses ( $LD_{50}$ s) in mice were 11.2, 16 and 62 mg/kg after IV, IP and SC administration respectively. The therapeutic index ( $LD_{50}/ED_{50}$ ) for fentanyl in mice was 775. The fentanyl  $LD_{50}$ s in rats were 18, 6 and 12 mg/kg after oral (PO), IV and SC administration respectively, and therapeutic index was 277-500. In dogs, the cardiovascular safety margin (IV dose producing severe cardiovascular side-effects including tachycardia, vasodilation, and depressed myocardial contractility: IV doses sufficient to produce deep surgical analgesia) was 5. The neurological safety margin (IV dose producing convulsions: dose producing deep surgical analgesia) was 160 and the metabolic safety margin was 60. The safety margin for fentanyl was greater than that for less potent and longer acting opioids in several studies.

Adverse reactions reported in humans were respiratory depression, hypotension, bradycardia, muscle and chest wall rigidity, pruritus, nausea and vomiting.

### Repeat Dose Toxicology and Carcinogenicity

No long-term studies, to assess fentanyl subchronic and chronic toxicity, and the carcinogenic potential of fentanyl in animals, have been reported in the literature.

### Reproductive Toxicology

Sea urchin eggs exposed to fentanyl at concentrations of 3.3 and 33 nM, showed no adverse effects on fertilization or cell division. No teratogenic effects were observed in fetal mice exposed to fentanyl (maternal doses 12-16 mg/kg, IP) on gestation day 9 and in rat pups exposed to fentanyl throughout gestation (continuous maternal doses up to 500  $\mu$ g/kg/d, SC by osmotic minipump). Fentanyl had embryocidal effects at 30  $\mu$ g/kg IV or 160  $\mu$ g/kg SC, and impaired fertility at 160  $\mu$ g/kg SC, when administered to rats for 12-21 days. In sheep, fentanyl had no effect on uterine blood flow and tone, and no cardiovascular and acid-base effects in maternal or fetal sheep at 50, 75 and 100  $\mu$ g IV on gestation days 124-138, measured for 2 hours post-drug administration.

**Genotoxicity****Report # RA/FC/96/002: Bacterial Reverse Mutation Assay**

**Purpose:** To evaluate the mutagenic potential of fentanyl citrate. In this assay, referred to as the Ames test, induction of reverse mutations in specific loci of *Salmonella typhimurium* and *E. coli* by exposure to fentanyl citrate, was measured both with and without metabolic activation (S-9).

**Experimental Design:** After dose selection in a preliminary toxicity assay at 6.7 - 5000 µg/plate, *Salmonella* tester strains TA98, TA100, TA1535, and TA1537 and *E. Coli* strain WP2uvrA were incubated with fentanyl citrate (0, 33, 100, 333, 1000, 3333, and 5000 µg/plate, 200 µl/plate) at 37 ± 2°C for 48-72 hours, with and without metabolic activation with liver microsomes (S-9). Revertant colonies were counted. The assay was conducted in triplicate.

**Metabolic Activation System:** Liver microsomal enzymes (S-9 homogenate) were prepared from Sprague-Dawley rats injected with Aroclor 1254 (500 mg/kg, IP). The S-9 mix consisted of 10% S-9 homogenate, 5 mM glucose-6-phosphate, 4 mM β-nicotinamide-adenine dinucleotide phosphate, 8 mM MgCl<sub>2</sub> and 33 mM KCl in 100 mM phosphate buffer at pH 7.4. The sham mix was 100 mM phosphate buffer alone at pH 7.4.

**Test Article:** Fentanyl citrate, USP Batch No. B0030-950701)

**Vehicle Control:** Sterile distilled water (CAS #7732-18-5)

**Positive Control without S-9:** TA98: 2-nitrofluorene (1.0 µg/plate, CAS # not provided,  
TA100, TA1535: sodium azide (1.0 µg/plate, CAS # not provided,  
TA1537: 9-aminoacridine (75 µg/plate, CAS #not provided,  
WP2uvrA: methyl methanesulfonate (1,000 µg/plate, CAS #not provided,

**Positive Control with S-9:** All strains: 2-aminoanthracene (1.0 µg/plate for all *Salmonella* strains, 10 µg/plate for WP2uvrA, CAS # not provided,

**Criteria for Positive Result:** A positive response was defined as a 3x increase in mean revertants in TA1535 and TA1537, and a 2x increase in mean revertants in TA98, TA100 and WP2uvrA compared to mean vehicle control values.

**Results:** In the toxicity assay, no precipitate and no toxicity at the maximum dose of 5 mg/plate. No positive responses were observed in any tester strain in the presence and

absence of S-9 metabolic activation.

**Evaluation:** Fentanyl citrate, at doses up to 5000 µg/plate (highest required dose in non-mammalian *in vitro* mutagenicity assays), was not mutagenic in the Bacterial Reverse Mutation Assay (Ames Test) in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia Coli* strain WP2uvrA, in the presence and in the absence of metabolic activation with Aroclor-induced rat liver S-9.

**Report #RA/FC/96/001: In Vitro Mammalian Cell Gene Mutation Test.**

**Purpose:** To evaluate the mutagenic potential of fentanyl citrate by measuring forward mutations at the thymidine kinase locus of L5178Y mouse lymphoma cells.

**Experimental Design:** After a preliminary toxicity assay (at 0.5-3500 µg/ml) to determine dose levels, L5178Y cells (clone 3.7.2C) were incubated with fentanyl citrate (0, 50, 100, 250, 500, and 600 µg/ml in the non-activated system, and 0, 100, 200, 300, 400 and 500 µg/ml in the activated system) with and without exogenous metabolic activation with S-9, at  $37 \pm 1^\circ\text{C}$  for 4 hours. The cells were washed, resuspended and incubated for 24-48 hours. The cells were plated and incubated for 10-14 days at  $37 \pm 1^\circ\text{C}$ , and then scored for expression of mutant colonies (chromosome aberrations associated with chromosome 11 at the TK locus) using an electronic cell counter. The assays were conducted in duplicate.

**Metabolic Activation System:** Liver microsomal enzymes (S-9 homogenate) were prepared from Sprague-Dawley rats injected with Aroclor 1254 (500 mg/kg, IP). The S-9 mix consisted of S-9 homogenate (250 µl) with cofactors in Fischer's Medium for Leukemic Cells of mice with 0.1% Pluronic (F<sub>6</sub>P), 6.0 mg β-nicotinamide-adenine dinucleotide phosphate, 11.25 mg DL-isocitric acid and 750 µl F<sub>6</sub>P/ ml at pH 7.0.

**Test Article:** Fentanyl citrate, USP      Batch #B0030-950701, 99.6% purity)

**Vehicle Control:** Sterile distilled water (CAS #7732-18-5,

**Positive Control without S-9:** Methyl methanesulfonate (MMS, CAS # 66-27-3, at 1000 and 2000 µg/ml.

**Positive Control with S-9:** 7,12-Dimethyl-benz(a)anthracene (7,12-DMBA, CAS #57-97-6, ) at 250 and 400 µg/ml.

**Criteria for Positive Result:**  $\geq 100$  mutants per  $10^6$  cells over background level.

**Results:** In the preliminary toxicity assay, there was no fentanyl citrate precipitate at up to 3500 µg/ml. Cytotoxicity was 100% at 1000 µg/ml. In the mutagenesis assay, the results were negative (mutant frequencies [mean # trifluorothymidine colonies/mean # viable count colonies, adjusted by a dilution factor] < 55 mutants per 10<sup>6</sup> clonable cells over the background level) for solvent control in the presence and absence of S-9 and negative for all concentrations of fentanyl citrate (50, 100, 250, 500, and 600 µg/ml) in the absence of S-9 activation. The results were equivocal (mutant frequencies 55-99 mutants per 10<sup>6</sup> clonable cells over the background level) for fentanyl citrate at all concentrations (100, 200, 300, 400 and 500 µg/ml) in the presence of S-9. The results were positive (mutant frequencies > 99 per 10<sup>6</sup> clonable cells over the background level) for positive controls.

**Evaluation:** Fentanyl citrate was not mutagenic in the L5178Y/TK<sup>+</sup> Mouse Lymphoma Mutagenesis Assay, either in the presence (at 100-500 µg/ml) or absence (at 50-600 µg/ml) of metabolic activation with S-9.

**Report #RA/FC/96/003: Micronucleus Cytogenetic Assay in Mice.**

**Purpose:** To evaluate the mutagenic potential of fentanyl citrate by measuring the incidence of fentanyl-induced micronucleated polychromatic erythrocytes in bone marrow of male and female mice.

**Experimental Design:** After a toxicity study to determine dose levels for the micronucleus assay, ICR mice (Harlan Sprague-Dawley, Inc., Frederick, MD, males 29.8-37.1 g, females 21.5-31.2 g, n = 5/sex/dose/collection time point + additional 5/sex at 48 mg/kg) were administered cyclophosphamide (60 mg/kg IP) or fentanyl citrate (0, 6, 12, 24, and 48 mg/kg IP in 10 ml/kg) and were observed for clinical signs of drug effect during the period between fentanyl administration and sacrifice at 24, 48 or 72 hours post-drug. After sacrifice, bone marrow cells from the femur were isolated, mounted on slides, fixed and stained with May-Gruenwald-Giemsa. The number of micronucleated normochromatic erythrocytes per 1000 polychromatic erythrocytes were counted. Bone marrow toxicity was determined by observing the proportion of polychromatic erythrocytes to total erythrocytes.

**Test Article:** Fentanyl citrate, USP      Batch #B0030-950701, 99.6% purity)

**Vehicle Control:** Sterile distilled water (CAS #7732-18-5,

**Positive Control:** Cyclophosphamide (CP, CAS #6055-19-2,

**Criteria for Positive Result:** Significantly greater number of micronucleated polychromatic erythrocytes in fentanyl or cyclophosphamide treated cells compared to vehicle control cells (at  $p \leq 0.05$ ) at all sampling times (24, 48 and 72 hours).

**Results:** Clinical signs in the toxicity assay were hyperactivity at all doses (2, 5, 16 and 48 mg/kg IP, males and females), prostration (48 mg/kg, males and females), and lethargy (48 mg/kg, males). One female mouse died after 48 mg/kg fentanyl. In the micronucleus assay, clinical signs were hyperactivity at all doses (6, 12, 24, and 48 mg/kg IP, males and females), prostration (24 and 48 mg/kg, males and females) and lethargy (48 mg/kg, males). Three of twenty males that were administered 48 mg/kg fentanyl died.

There were no significant increases in micronucleated polychromatic erythrocytes in male or female mice in any group that received fentanyl (12, 24, or 48 mg/kg IP) compared to vehicle control animals, at 24, 48 or 72 hours post-drug administration. Micronucleated polychromatic erythrocytes increased significantly in cyclophosphamide (60 mg/kg IP) treated male and female mice compared to vehicle control mice, at 24 hours after drug administration.

**Evaluation:** In the toxicity assay, the Maximum Tolerated Dose (MTD) for fentanyl citrate in male and female mice was 48 mg/kg. In the micronucleus assay, male mice (9/15 at 24 mg/kg IP and 12/20 at 48 mg/kg IP) were more sensitive than female mice (0/15 at 24 mg/kg IP and 0/20 at 48 mg/kg IP) to fentanyl citrate induced lethargy. Male mice (3/20) were more sensitive to lethal effects than were female mice (0/20) of fentanyl citrate at 48 mg/kg IP.

There was a significant cyclophosphamide-induced (60 mg/kg IP) increase in micronucleated polychromatic erythrocytes compared to vehicle controls at 24 hours post-drug. No significant differences in the numbers of micronucleated polychromatic erythrocytes were observed after fentanyl citrate (12-48 mg/kg IP) compared to control values in the Mouse Micronucleus Cytogenetic Assay.

## Summary of Genotoxicity Studies

Test	Strain	Fentanyl Citrate Concentrations	Metabolic Activation (S-9)	Positive Controls	Results	
Bacterial Reverse Mutation Assay	<i>Salmonella strains:</i> TA98 TA100 TA1535 TA1537	0, 33, 100, 333, 1000, 3333, 5000 µg/plate	+	2-aminoanthracene	-	
			-	2-nitrofluorene	-	
			+	2-aminoanthracene sodium azide	-	
			-	2-aminoanthracene sodium azide	-	
			+	2-aminoanthracene	-	
	<i>E-coli tester strain</i> WP2uvrA			-	9-aminoacridine	-
				+	2-aminoanthracene	-
				-	4-nitroquinoline-N-oxide	-
				+	7,12 dimethylbenz(a)anthracene	-
				-	methyl methanesulfonate	-
In Vitro Mammalian Cell Gene Mutation Test	L5178Y TK +/- mouse lymphoma	50,100,200,250,300,400,500,600 µg/ml	+	7,12 dimethylbenz(a)anthracene	-	
			-	methyl methanesulfonate	-	
Micronucleus Cytogenetic Assay	ICR mouse bone marrow polychromatic erythrocytes	0, 6, 12, 24, 48 mg/kg IP	Not applicable	cyclophosphamide	-	

## Special Toxicology Studies

Fentanyl (10-50 ng/ml) exposure, *in vitro*, for 48 hours in rat cardiomyocytes increased the spontaneous beating rate, cell growth, protein synthesis and atrial natriuretic peptide secretion. Fentanyl-induced ANP secretion, but not beating rate or protein synthesis, was inhibited by naloxone ( $10^{-6}$  M). In human cells (source not disclosed), fentanyl (up to 250 µM) inhibited nucleic acid and protein synthesis and cell growth.

Local irritation and sensitization studies were not conducted in animals because no suitable animal model for oral transmucosal delivery of fentanyl could be developed, in the opinion of the sponsor. Local irritant effects and sensitization were to be evaluated in the clinical studies.

Redacted

1

pages of trade

secret and/or

confidential

commercial

information

---

## OVERALL SUMMARY AND DISCUSSION

### Pharmacology

The efficacy of fentanyl citrate analgesia in mice, rats, rabbits, dogs, monkeys and other species, has been well established and widely reported in the literature. Maximal analgesia was reported in dogs at a plasma fentanyl concentration of 30 ng/ml, and in Rhesus monkeys at 43.4 ng/ml. Preclinical data supporting the efficacy of Actiq™ were not reported by the sponsor because an animal model for oral transmucosal fentanyl administration was not developed. However, there is substantial data supporting the efficacy of OTFC in humans from clinical trials testing Fentanyl Oralet® (NDA 20-195) and Actiq™.

The pharmacological effects of fentanyl are mediated primarily through interaction with  $\mu$ 1- (high affinity) and  $\mu$ 2- (low affinity) opioid receptors in the central nervous system, and to a lesser extent with central and peripheral (e.g. vascular)  $\alpha$ -adrenergic and  $M_3$  muscarinic receptors. Secondary effects of fentanyl in rodents include increased motor activity and circling, Straub tail, increased muscle tone and mydriasis, and in dogs include decreased motor activity, ataxia, depressed responsiveness to auditory or painful stimuli, bradycardia, respiratory depression, salivation and defecation. In humans, fentanyl side effects include respiratory depression, hypotension, bradycardia, muscle/chest wall rigidity, pruritus, nausea and vomiting.

Tolerance to the analgesic and secondary effects of fentanyl was demonstrated in preclinical studies. Concomitant exposure to painful stimuli, and intermittent, rather than continuous exposure to fentanyl, decreased the development of tolerance. Indices of physical dependence on fentanyl were observed *in vitro* and *in vivo*. Observations included withdrawal contractures in guinea pig ileal longitudinal muscle, and increased arterial blood pressure responses in to somatic nerve stimulation in dogs. Fentanyl abuse liability was not addressed in preclinical studies. There are literature reports that laboratory animals will self-administer other mu-opioid agonist drugs (e.g. morphine), and fentanyl abuse has been reported in humans.

Fentanyl analgesic effects were potentiated by the calcium blockers clonidine, verapamil and KB-2796 (N-type), and the  $\alpha$ 2-adrenergic agonists dexmedetomidine and medetomidine in rats, the benzodiazepine midazolam and tricyclic antidepressant imipramine in rabbits, the barbiturate pentobarbital in lambs and the dopaminergic neuroleptic drugs droperidol and zuclopenthixol in sheep. Midazolam and imipramine had no effect on fentanyl respiratory depression, but pentobarbital increased peripheral and central hemodynamic effects of fentanyl. The muscle relaxant effects of the non-depolarizing neuromuscular blocking agent ORG 9426 were not altered by fentanyl in cats. Antagonism of fentanyl-induced analgesia or side effects (e.g. muscular rigidity, respiratory depression or cardiovascular effects) was produced by  $\alpha$ 1-adrenergic receptor antagonism with prazosin and benzodiazepine receptor antagonism with 3-HMC in rats, naloxone in rabbits and dogs, and the antimuscarinic agent atropine in dogs.

#### SAFETY PHARMACOLOGY

Preclinical studies, in rats, dogs, pigs and other animals have shown that fentanyl can decrease heart rate and blood pressure. In dogs, fentanyl (50  $\mu$ g/kg IV) had no effect on atrial filling pressure, left ventricular end-diastolic pressure, cardiac output, stroke volume, left ventricular dP/dt and total body oxygen consumption. In lambs, fentanyl (4.4 mg/kg IV) increased respiratory depression, arterial CO<sub>2</sub> tension and decreased arterial O<sub>2</sub> tension and renal blood flow without effect on cardiac output, heart rate, mean arterial blood pressure and blood flow to digestive organs, muscles and skin. Fentanyl (50  $\mu$ g/kg IV) decreased coronary circulation and myocardial metabolism in dogs, but not in tests on isolated canine coronary rings (at 100 ng/ml), isolated rat hearts (at 100 mg/ml) and in intact pigs (300  $\mu$ g/kg IV).

Fentanyl decreased overall cerebral blood flow (35%) and cerebral oxygen metabolism (50%) in rats (at 100  $\mu$ g/kg IV) but not in neonatal lambs (at 4.4 mg/kg IV). However, in the lambs, blood flow decreased locally in the spinal cord, cerebellum, medulla, diencephalon and subcortical white matter, in response to fentanyl. This effect was naloxone reversible.

Fentanyl induced respiratory depression in animal studies, indicated by increased paCO<sub>2</sub> in rabbits (11.5  $\mu$ g/kg IV), and decreased respiratory minute volume, respiratory rate and tidal volume, and increased end-tidal CO<sub>2</sub> in dogs (10-40  $\mu$ g/kg IV). These effects were reversed with controlled or assisted ventilation and naloxone administration.

No fentanyl-induced hepatotoxicity was observed in isolated rat hepatocytes (74.3 and 148 nM). Repeated intraperitoneal fentanyl (15.6 µg/kg IP, q.d. for 6 days) administration in rats increased SGPT, but not SGOT. Overall, no hepatocellular damage or liver necrosis was observed following fentanyl administration in rats (up to 350 µg/kg IV over 3 hours).

Fentanyl administration produced antidiuretic-like effects in dogs, indicated by decreased urine volume, glomerular filtration rate and renal plasma flow, and increased renal vascular resistance at 25 µg/kg IV, and decreased urine output and free water clearance, and increased urine osmolarity at 0.1-1.0 mg/kg IV in another study. Fentanyl (10 µg/kg IV) increased growth hormone secretion in male rats. In isolated rat cardiomyocytes, fentanyl (10-50 ng/ml) increased atrial natriuretic peptide release, growth and development of contractile elements, protein biosynthesis and the spontaneous beating rate.

### PHARMACOKINETICS

The maximum plasma concentration, bioavailability and permeability coefficient increased by 3x to 5x with increasing basicity of the buccal fentanyl solution in dogs. In dogs, the terminal elimination half life was similar after intravenous and buccal administration. The T<sub>max</sub> for all buccal solutions with pH 6.6-7.7 was within 10 minutes of system removal.

In healthy male volunteers, a single dose of transmucosal fentanyl (15 µg/kg over 15 minutes) resulted in a T<sub>max</sub> of 23 minutes (range                    minutes), C<sub>max</sub> of 2.7 ng/ml (range                    ng/ml), half-life of 6.6 hours (range                    hours), total plasma clearance of 0.5 L/hr/kg (range                    L/hr/kg), total body clearance of approximately 13.3 ml/kg/min, and bioavailability of 50% (range                    %). The volume of distribution was 3-6 L/kg and terminal elimination half-life 219 minutes in opioid non-tolerant adults. The onset of action was approximately 5 minutes (range                    minutes).

### ADME

Absorption of buccal fentanyl was rapid in dogs, with detection of the drug in plasma at 6 minutes and maximum plasma levels at 10 minutes after drug administration. Increasing the pH of the fentanyl solution increased buccal absorption, bioavailability and permeability 3x-5x. No depot effect, buccal adsorption or buccal metabolism of fentanyl was found. In clinical studies, OTFC bioavailability was 50%, including 25% from the buccal mucosa and absorption of 1/3 of the remaining 75% swallowed fentanyl. The remaining swallowed fentanyl underwent hepatic and duodenal first-pass metabolism.

Fentanyl (IV) plasma concentration was equivalent with brain, heart and lung concentrations at 1.5 minutes, and with muscle and fat at 120 minutes, with lower concentrations detected in liver, gastric contents, small intestine and kidneys in rats. Affinities for fentanyl were 4:1 in muscle, 5:1 in brain, and 35:1 in fat, suggesting potential accumulation with repeated administration. In humans, the fentanyl concentration-time curve was described by a three-compartment model. Fentanyl distributed to human brain, lung, kidney, spleen and heart with a rapid distribution phase

half-life, slow distribution phase half-life and terminal elimination half-life of 1.7, 13 and 219 minutes respectively. Fentanyl crossed rabbit, sheep and human placenta resulting in fetal/maternal plasma fentanyl ratios of 0.3, 0.33 and 0.8 respectively. Fentanyl metabolites phenylacetic acid, norfentanyl and p-hydroxy (phenethyl) fentanyl distributed to gastric contents, brain, heart, lung, liver, kidney, muscle and fat in rats. Fentanyl plasma protein binding, predominantly to alpha-1-acid glycoprotein with minor binding to albumin and lipoproteins, was approximately 60-80% in rabbits and dogs, and 80% in humans.

Fentanyl was metabolized in mouse liver, and to a lesser extent kidney and adrenal gland, to norfentanyl, phenylacetic acid, p-hydroxy (phenethyl) fentanyl and three additional minor metabolites. In rats, the major metabolic pathway was hepatic oxidative N-dealkylation to norfentanyl and phenylacetic acid, and small amounts of p-hydroxy (phenethyl) fentanyl. Additional fentanyl metabolic pathways in the rat were amide hydrolysis, hydroxylation and conjugation. After IV administration of 3H-fentanyl, 25% radiolabel was detected as metabolites at 15 minutes, and 80% as metabolites at 4 hours.

Fentanyl undergoes extensive and rapid metabolism in humans. In one study, more than 80% of an intravenous dose of fentanyl was recovered as metabolites (76% in urine and 8% in feces). Metabolites were detected in plasma within two minutes of drug administration, and exceeded parent drug after 30 minutes. Early clinical studies identified norfentanyl [4-N-(N-propionylanilino)piperidine] and despropionylfentanyl [1-(2-phenylethyl)-4-N-analinopiperidine] in plasma and norfentanyl [4-N-(N-propionylanilino)piperidine], hydroxyfentanyl [1-(2-phenylethyl)-4-N-(hydroxypropionylanilino)piperidine], and hydroxynorfentanyl [4-N-(N-hydroxypropionylanilino)-piperidine] in urine after fentanyl administration. Fentanyl metabolism in humans was further characterized in a study described in *Report #CR/FC/96/001*. This investigation found: In liver microsomes, the major metabolite detected was norfentanyl (1440 pmol/min/mg) representing 99% of all metabolites, followed by despropionylfentanyl (1.1 pmol/min/mg) and hydroxyfentanyl (0.58 pmol/min/mg). Hydroxynorfentanyl was detected after 90 minutes, but not after 7 minutes incubation of microsomes with fentanyl. In human duodenal microsomes, norfentanyl (0.01-0.41 nmol/min/mg) was the detected after incubation with fentanyl.

In the microsomes containing cDNA-expressed cytochrome P450 isoforms, those containing P450 3A4 had the highest rate of norfentanyl formation, at 61 pmol/min/mg protein. Further, addition of troleandomycin and midazolam decreased formation of norfentanyl 63% and 99% respectively in liver microsomes, indicating that the P450 3A4 isoform was the major enzyme responsible for the transformation. In duodenal microsomes, troleandomycin and midazolam inhibited norfentanyl formation 55%-78% and 35%-56% respectively. Norfentanyl formation was inhibited by diethyldithiocarbamate but not by coumarin and 4-methylpyrazole. No other inhibitor decreased norfentanyl formation.

Fentanyl was excreted predominantly as metabolites in urine and to a lesser extent in feces in preclinical studies. For example, after intravenous administration in dogs, 32% [<sup>3</sup>H]-fentanyl was excreted in urine, with 4%-6% excreted as unchanged fentanyl, during the first 6 hours. After intravenous fentanyl administration in humans, less than 8% of the total dose was eliminated unchanged (6% in urine and 1% in feces), while approximately

75% intravenous dose was excreted in urine and 9% in feces as metabolites.

## TOXICOLOGY

Preclinical single dose toxicology studies on OTFC were not performed because a suitable animal model for this route of administration could not be developed, in the opinion of the sponsor. The profile of acute fentanyl toxicity by other routes is well established. Single dose studies demonstrated relatively low toxicity and a high therapeutic index ( $LD_{50}/ED_{50}$ , 31.3 relative to morphine) for fentanyl. The  $LD_{50}$ s in mice were 11.2, 16 and 62 mg/kg, and in rats were 18, 6 and 12 mg/kg after IV, IP and SC administration respectively. The therapeutic index was 775 in mice and 277-500 in rats. In dogs, the cardiovascular safety margin was 5, neurological safety margin was 160 and metabolic safety margin was 60. Adverse reactions reported in humans were respiratory depression, apnea, rigidity, bradycardia, hypertension or hypotension, blurred vision, dizziness, emesis, nausea, laryngospasm and diaphoresis.

No long-term preclinical studies, to assess fentanyl subchronic and chronic toxicity and carcinogenic potential have been reported in the literature.

Fentanyl (up to 33 nM) had no effect on sea urchin egg fertilization or cell division, and no teratogenic effects in fetal mice (maternal doses 12-16 mg/kg IP, gestation day [gd] 9) or rats (500  $\mu$ g/kg/d continuous SC throughout gestation). Fentanyl was embryocidal (30  $\mu$ g/kg IV or 160  $\mu$ g/kg SC, gd 12-21) and impaired fertility (160  $\mu$ g/kg SC, gd 12-21) in rats. In sheep fentanyl (50-100  $\mu$ g IV, gd 124-138) had no effects on uterine blood flow and tone, and no cardiovascular and acid-base effects in maternal or fetal sheep for 2 hours post-drug administration.

In the mutagenicity studies, fentanyl citrate, at doses up to 5000  $\mu$ g/plate, was not mutagenic in the Bacterial Reverse Mutation Assay (Ames Test) in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia Coli* strain WP2uvrA, in the presence and in the absence of metabolic activation with Aroclor-induced rat liver S-9. Fentanyl was not mutagenic in the L5178Y/TK<sup>+</sup> Mouse Lymphoma Mutagenesis Assay, either in the presence (at 100-500  $\mu$ g/ml) or absence (at 50-600  $\mu$ g/ml) of metabolic activation with S-9. No significant differences in the numbers of micronucleated polychromatic erythrocytes were observed after fentanyl citrate (12-48 mg/kg IP) compared to control values in the Mouse Micronucleus Cytogenetic Assay. The doses evaluated were determined appropriately by dose selection/ toxicity tests. All mutagenicity assays were replicated, and positive and negative controls were appropriate. The proposed package label has been revised to include the results of the mutagenicity tests reported in the present application.

Fentanyl increased the spontaneous beating rate, cell growth, protein synthesis and ANP secretion in rat cardiomyocytes, and decreased nucleic acid and protein synthesis and cell growth in a human cell line. These effects may be relevant in the case of long-term contact (e.g. transdermal application) only, in the opinion of the sponsor. Local irritation and sensitization studies were not conducted in animals because a suitable animal model

for oral transmucosal delivery of fentanyl was unavailable, in the opinion of the sponsor. Local irritant effects and sensitization were to be evaluated in the clinical studies.

### CONCLUSIONS

- Fentanyl efficacy is well documented in the literature; efficacy of oral transmucosal fentanyl citrate has been demonstrated from the marketing experience of Oralet<sup>®</sup> and in clinical studies testing Actiq<sup>™</sup>.
- Fentanyl effects mediated primarily through CNS  $\mu$ -opioid receptors.
- Secondary effects: In rats, increased motor activity, circling, Straub tail, increased muscle tone and mydriasis; In dogs, decreased motor activity, ataxia, depressed responsiveness to auditory/painful stimuli, bradycardia, respiratory depression, salivation and defecation; In humans, respiratory depression, hypotension, bradycardia, muscle/chest wall rigidity, pruritus, nausea and vomiting.
- Tolerance development attenuated by exposure to painful stimuli and intermittent, rather than continuous fentanyl exposure.
- Indices of physical dependence on fentanyl observed *in vitro* in isolated guinea pig ileal longitudinal muscle (withdrawal contractures), and *in vivo* in dogs (increased blood pressure responses to somatic nerve stimulation).
- Fentanyl abuse liability suggested by self-administration of  $\mu$ -opioid drugs by laboratory animals, and reports of fentanyl abuse by humans in the literature.
- Fentanyl analgesia potentiated by: calcium blockers,  $\alpha$ 2-adrenergic agonists, benzodiazepine, barbiturates and dopaminergic neuroleptic drugs, and antagonized by  $\alpha$ 1-adrenergic antagonists,  $\mu$ -opioid receptor antagonists and antimuscarinic agents.
- Secondary fentanyl effects in rats, dogs, pigs and lambs: decreased heart rate, blood pressure, arterial O<sub>2</sub> tension, renal blood flow, coronary circulation, myocardial metabolism, overall cerebral blood flow and cerebral oxygen metabolism, and increased respiratory depression and arterial CO<sub>2</sub> tension. Fentanyl had antidiuretic-like effects in dogs and increased growth hormone secretion in rats.
- Rapid absorption of buccal fentanyl in dogs. In dogs the C<sub>max</sub>, bioavailability and permeability coefficient after buccal fentanyl increased (3x-5x) with increasing drug solution pH. Bioavailability in dogs ranged from approximately 20% to 57% for fentanyl solutions between pH 6.6-7.7 respectively. In comparison, bioavailability in humans is approximately 50%. No difference in terminal elimination half-life between IV and buccal fentanyl, T<sub>max</sub> for buccal administration (pH 6.6-7.7) was 10 minutes within system removal in dogs.

- Fentanyl and metabolites rapidly distributed to brain, heart, lung, muscle, fat, liver, kidney. Affinity for fentanyl 4:1 in muscle, 5:1 in brain, 35:1 in fat, suggesting potential accumulation with repeated administration. Plasma protein binding to  $\alpha$ -1-acid glycoprotein, albumin and lipoproteins 60-80% in animals, 80% in humans. Short duration of fentanyl effect due in part to rapid redistribution to storage sites in muscle and fat, and rapid hepatic metabolism.
- The major metabolic pathway in rats and humans: oxidative N-dealkylation of fentanyl to norfentanyl (99% of all metabolites) by P450 3A4 isozymes, in rat and human liver and in human duodenum. Minor pathways in rats and humans include amide hydrolysis to despropionylfentanyl and alkyl hydroxylation to hydroxyfentanyl. Hydroxyfentanyl further underwent N-dealkylation to hydroxynorfentanyl in human hepatic microsomes. Metabolism rapid (detection at 2 minutes and levels exceeding parent drug at 30 minutes in humans) and extensive (80% of parent drug in humans).
- Fentanyl excreted predominantly as metabolites in urine (75% IV dose) and feces (9% IV dose), less than 8% eliminated unchanged (6% in urine, 1% in feces).
- No animal model developed for preclinical toxicology studies on OTFC. Acute fentanyl toxicology by other routes well established and reported in the literature. LD<sub>50</sub>: 11.2 (IV), 16 (IP) and 62 (SC) mg/kg in mice, 18 (IV), 6 (IP) and 12 (SC) mg/kg in rats. Low toxicity and high therapeutic index (31.3 relative to morphine). TI: 775 in mice, 277-500 in rats. In dogs, cardiovascular safety margin 5, neurological safety margin 160, metabolic safety margin 60. Acute toxicity in humans include respiratory depression, apnea, rigidity, bradycardia, hypotension, emesis, nausea. No preclinical subchronic and chronic toxicology, and carcinogenicity studies for fentanyl reported in the literature.
- No teratogenic effects in fetal mice (maternal doses 12-16 mg/kg IP, gd 9) or rats 500  $\mu$ g/kg/d SC, throughout gestation). Embryocidal (30  $\mu$ g/kg IV or 160  $\mu$ g/kg SC, gd 12-21) and impaired fertility (160  $\mu$ g/kg SC, gd 12-21) in rats.
- Fentanyl citrate not mutagenic in the Ames bacterial Reverse Mutation Assay in *Salmonella* and *E. coli* (up to 5000  $\mu$ g/plate), in the L5178Y/TK<sup>+</sup> Mouse Lymphoma Mutagenesis Assay in the presence (100-500  $\mu$ g/ml) or absence (50-600  $\mu$ g/ml) of metabolic activation with S9, or in the Mouse Micronucleus Cytogenetic Assay (12-48 mg/kg IP).
- Local irritant effects and sensitization were evaluated clinically, since suitable animal models are not readily available.

**RECOMMENDATIONS**

**Actiq is approvable from a pharmacology and toxicology perspective, pending revision of the package insert as described below.**

Draft of pharmacology portion of letter to sponsor:

Copy under recommendations.

ISI 5/7/97  
Kathleen A. Haberny, Ph.D.  
ISI 5/8/97  
Team Leader: Dou H. (Lucy) Jean, Ph.D.

cc: IND Arch 20-747  
HFD 170/Division File  
HFD 170 /M. Wright Nolan  
HFD 170/ K Haberny

NDA 20-747

1

**Pharmacology/Toxicology Review  
Division of Anesthetic, Critical Care & Addiction Drug Products  
HFD-170/Kathleen Haberny**

**NDA: 20-747      A-018 / October 1, 1997 / Amendment to Pending Application**

**Information to sponsor    Yes (✓)    No ( )**

**Completion Date: October 7, 1997**

**Sponsor:            Anesta Corporation  
                          4745 Wiley Post Way, Suite 650  
                          Salt Lake City, UT 84116**

**Drug Name: Actiq™ (Oral Transmucosal Fentanyl Citrate)**

**Chemical Name: N (1-Phenethyl-piperidyl) propionanilide citrate**

**Drug Class: Synthetic phenyl piperidine derivative, opioid analgesic**

**Indication: Management of chronic pain, particularly breakthrough pain, in opioid tolerant patients**

**Route of Administration: Oral/Transmucosal**

**LABELING REVIEW**

In reference to the revised text for the physician and patient package inserts, proposed in NDA 20-747; Amendment A-018; the deficiencies previously identified in the Pharmacology/Toxicology Review and Evaluation of the Revised Package Insert, November 11, 1996, have not been addressed by the sponsor.

**RECOMMENDATIONS**

The deficiencies previously identified in the Pharmacology/Toxicology Review and Evaluation of the Revised Package Insert, November 11, 1996, have not been addressed in the revised text for the physician and patient package inserts, proposed in NDA 20-747; Amendment A-018. The following changes to the proposed package insert are recommended.

The currently approved label for Fentanyl Oralet® (Oral Transmucosal Fentanyl Citrate) contains the following statements on results of the reproduction studies:

"Reproduction studies in rats revealed a significant decrease in the pregnancy rate of all experimental groups. This decrease was most pronounced in the high dose group (1.25 mg/kg) in which one of twenty animals became pregnant. "

These statements should be included in the label for Actiq.

2. The statement in the currently approved label for OTFC,

"This high dose is approximately 180 x the maximum recommended human dose of 400 mcg for a 60-kg patient."

should not be included in the proposed label for Actiq. The estimation of human dose multiples for transmucosal fentanyl based on animal data obtained from intravenous or subcutaneous administration is inappropriate.

3. The statements in the proposed label,

**Draft of pharmacology portion of letter to sponsor:**

Copy under Recommendations.

*ISI*  
\_\_\_\_\_  
Kathleen A. Haberny, Ph.D. *10/7/97*

*ISI*  
\_\_\_\_\_  
Team Leader: Dou H. Jean, Ph.D. *10/7/97*

cc: IND Arch  
HFD 170/Division File  
HFD 170 /K Nolan  
HFD 170/ K Haberny