CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74917

Trade Name Fentanyl Citate Injection USP 0.05mg/ml

Generic Name Fentanyl Citrate Injection USP 0.05mg/ml

Sponsor Marsam Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74917

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Administrative Document(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74917

APPROVAL LETTER

ANDA 74-917

FEB 3 1998

Marsam Pharmaceuticals Inc.
Attention: Steven W. Brown, R.Ph.
Building 31, 24 Olney Avenue
P.O. Box 1022
Cherry Hill, New Jersey 08034

Dear Sir:

This is in reference to your abbreviated new drug application dated June 26, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Fentanyl Citrate Injection USP, 0.05 mg (base)/mL, packaged in single-dose vials.

Reference is also made to your amendment dated July 25, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Fentanyl Citrate Injection, 0.05 mg (base)/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Sublimaze® Injection, 0.05 mg (base)/mL, of Janssen Pharmaceutica Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

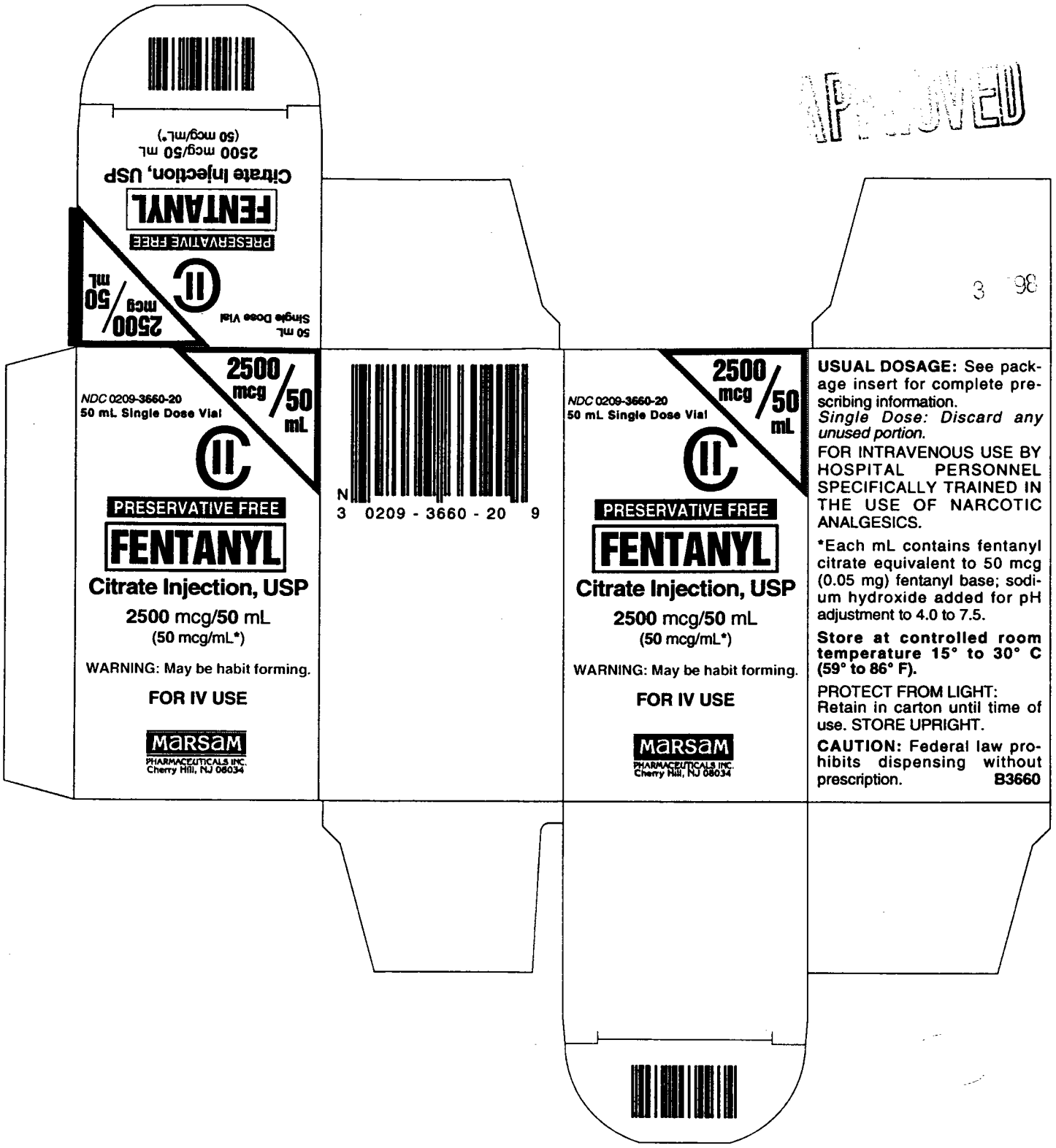
2/3/98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

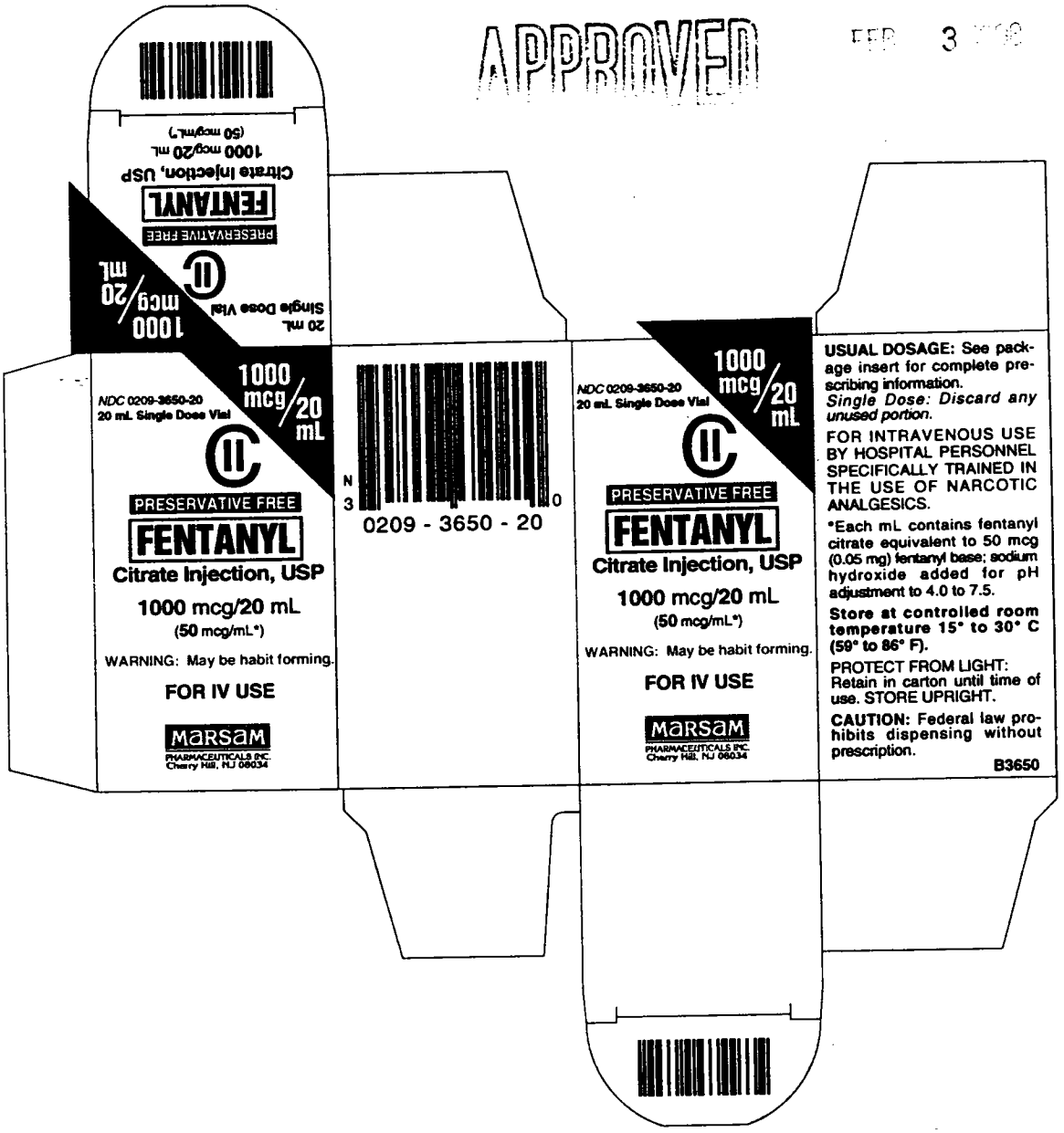
APPLICATION NUMBER 74917

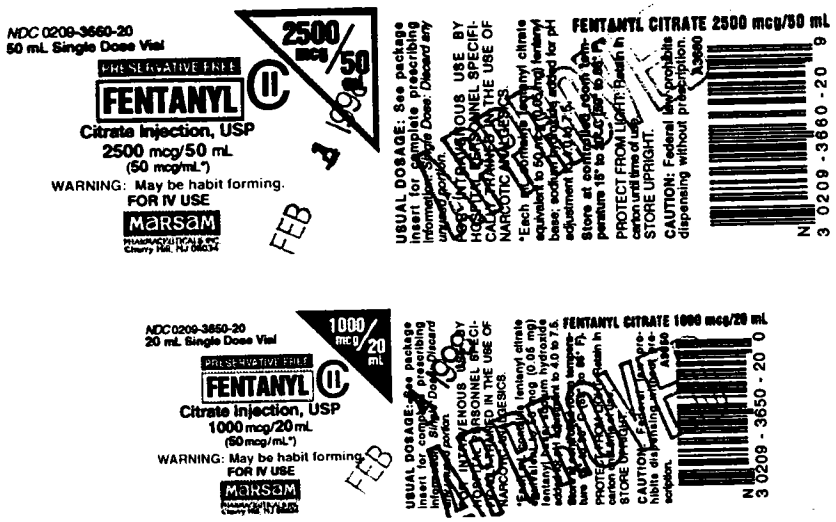
FINAL PRINTED LABELING


APPROVED
3 98
2500 mcg/50 mL
(50 mcg/mL*)
Citrate Injection, USP
FENTANYL
PRESERVATIVE FREE
50 mL
Single Dose Vial
NDC 0209-3660-20
50 mL Single Dose Vial
2500 mcg/50 mL
PRESERVATIVE FREE
FENTANYL
Citrate Injection, USP
2500 mcg/50 mL
(50 mcg/mL*)
WARNING: May be habit forming.
FOR IV USE
MARSAM
PHARMACEUTICALS INC.
Cherry Hill, NJ 08034
N
3 0209 - 3660 - 20 9
USUAL DOSAGE: See package insert for complete prescribing information.
Single Dose: Discard any unused portion.
FOR INTRAVENOUS USE BY HOSPITAL PERSONNEL SPECIFICALLY TRAINED IN THE USE OF NARCOTIC ANALGESICS.
*Each mL contains fentanyl citrate equivalent to 50 mcg (0.05 mg) fentanyl base; sodium hydroxide added for pH adjustment to 4.0 to 7.5.
Store at controlled room temperature 15° to 30° C (59° to 86° F).
PROTECT FROM LIGHT: Retain in carton until time of use. STORE UPRIGHT.
CAUTION: Federal law prohibits dispensing without prescription.
B3660

APPROVED

FEB 3




NDC 0209-3660-20
50 mL Single Dose Vial
PRESERVATIVE FREE
FENTANYL
CII
Citrate Injection, USP
2500 mcg/50 mL
(50 mcg/mL*)
WARNING: May be habit forming.
FOR IV USE
marsam
2500 mcg/50 mL
FEB
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PROTECT FROM LIGHT. Retain in carton until time of use.
STORE UPRIGHT.
CAUTION: Federal law prohibits dispensing without prescription.
FENTANYL CITRATE 2500 mcg/50 mL
N 3 0209 -3660 - 20 9

NDC 0209-3650-20
20 mL Single Dose Vial
PRESERVATIVE FREE
FENTANYL
CII
Citrate Injection, USP
1000 mcg/20 mL
(50 mcg/mL*)
WARNING: May be habit forming.
FOR IV USE
marsam
1000 mcg/20 mL
FEB
USUAL DOSAGE: See package insert for complete prescribing information. Single Dose. Discard any unused portion.
FOR INTRAVENOUS USE BY HOSPITAL PERSONNEL SPECIFICALLY TRAINED IN THE USE OF NARCOTIC ANALGESICS.
PROTECT FROM LIGHT. Retain in carton until time of use.
STORE UPRIGHT.
CAUTION: Federal law prohibits dispensing without prescription.
FENTANYL CITRATE 1000 mcg/20 mL
N 3 0209 - 3650 - 20 0

MARSAM PHARMACEUTICALS INC.

C3100

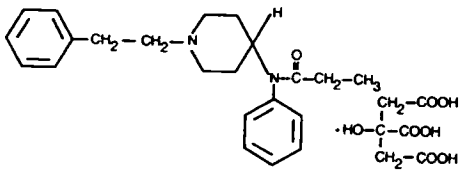
FENTANYL CITRATE INJECTION, USP

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION

Fentanyl Citrate Injection, USP is a potent narcotic analgesic. Each milliliter of solution contains fentanyl citrate equivalent to 50 mcg of fentanyl base, adjusted to pH 4.0 to 7.5 with sodium hydroxide. Fentanyl Citrate, USP, is a white, crystalline powder or white, glistening crystals, and is chemically identified as *N*-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1).

Fentanyl Citrate has the following structural formula:



$C_{22}H_{28}N_2O \cdot C_6H_8O_7$ M.W. 528.61

Fentanyl Citrate Injection is a sterile, non-pyrogenic, preservative free aqueous solution for intravenous or intramuscular injection.

CLINICAL PHARMACOLOGY

Fentanyl citrate is a narcotic analgesic. A dose of 100 mcg (0.1 mg) (2 mL) is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than either morphine or meperidine. Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl. Recent assays in man show no clinically significant histamine release in dosages up to 50 mcg/kg (0.05 mg/kg) (1 mL/kg). Fentanyl preserves cardiac stability, and blunts stress-related hormonal changes at higher doses.

The pharmacokinetics of fentanyl can be described as a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. The volume of distribution for fentanyl is 4 L/kg.

Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. It accumulates in skeletal muscle and fat, and is released slowly into the blood. Fentanyl, which is primarily transformed in the liver, demonstrates a high first pass clearance and releases approximately 75% of an intravenous dose in urine, mostly as metabolites with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single intravenous dose of up to 100 mcg (0.1 mg) (2 mL). Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is one to two hours. As with longer acting narcotic analgesics, the duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO_2 stimulation following administration of fentanyl citrate to man.

1. DIMINISHED SENSITIVITY TO CO_2 STIMULATION MAY PERSIST LONGER THAN DEPRESSION OF RESPIRATORY RATE. (Altered sensitivity to CO_2 stimulation has been demonstrated for up to four hours following a single dose of 600 mcg (0.6 mg) (12 mL) fentanyl citrate to healthy volunteers.) Fentanyl frequently slows the respiratory rate, duration and degree of respiratory depression being dose related.
2. The peak respiratory depressant effect of a single intravenous dose of fentanyl citrate is noted 5 to 15 minutes following injection. See also **WARNINGS** and **PRECAUTIONS** concerning respiratory depression.

INDICATIONS AND USAGE

Fentanyl Citrate Injection, USP is indicated in the following:

- for analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
- for use as a narcotic analgesic supplement in general or regional anesthesia.
- for administration with a neuroleptic such as droperidol injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.
- for use as an anesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

CONTRAINDICATIONS

Fentanyl citrate is contraindicated in patients with known intolerance to the drug or other opioid agonists.

WARNINGS

FENTANYL CITRATE SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS ANESTHETICS AND MANAGEMENT OF THE RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

See also discussion of narcotic antagonists in **PRECAUTIONS** and **OVERDOSAGE**.

If fentanyl is administered with a tranquilizer such as droperidol, the user should become familiar with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available.

As with other potent narcotics, the respiratory depressant effect of fentanyl may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. This rigidity has been reported to occur or recur infrequently in the extended postoperative period usually following high dose administration. In addition, skeletal muscle movements of various groups in the extremities, neck and external eye have been reported during induction of anesthesia with fentanyl; these reported movements have, on rare occasions, been strong enough to pose patient management problems. This effect is related to the dose and speed of injection and its incidence can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of fentanyl citrate; 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when fentanyl citrate is used in anesthetic doses titrated by slow intravenous infusion; or, 3) simultaneous administration of fentanyl citrate and a full paralyzing dose of a neuromuscular blocking agent when fentanyl is used in rapidly administered anesthetic dosages. The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status.

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Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of fentanyl. Where moderate or high doses are used (above 10 mcg/kg), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received fentanyl. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Fentanyl may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia and bronchoconstriction.

Severe and unpredictable potentiation by MAO inhibitors has been reported for other narcotic analgesics. Although this has not been reported for fentanyl, there are insufficient data to establish that this does not occur with fentanyl. Therefore, when fentanyl is administered to patients who have received MAO inhibitors within 14 days, appropriate monitoring and ready availability of vasodilators and beta-blockers for the treatment of hypertension is indicated.

Head Injuries and Increased Intracranial Pressure- Fentanyl should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, fentanyl may obscure the clinical course of patients with head injury.

PRECAUTIONS

General

The initial dose of fentanyl citrate should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses.

Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see CLINICAL PHARMACOLOGY) fentanyl can also alter respiration. Therefore, when fentanyl is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When a tranquilizer such as droperidol is used with fentanyl, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of fentanyl are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

When fentanyl is used with a tranquilizer such as droperidol, hypotension can occur. If it occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of droperidol, epinephrine may paradoxically decrease the blood pressure in patients treated with droperidol.

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of fentanyl citrate combined with droperidol. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

When droperidol is used with fentanyl and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Vital signs should be monitored routinely.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by fentanyl may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Respiratory depression secondary to chest wall rigidity has been reported in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Impaired Respiration

Fentanyl should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function

Fentanyl citrate should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

Cardiovascular Effects

Fentanyl may produce bradycardia, which may be treated with atropine. Fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

Drug Interactions

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics and general anesthetics) will have additive or potentiating effects with fentanyl. When patients have received such drugs, the dose of fentanyl required will be less than usual. Following the administration of fentanyl citrate, the dose of other CNS depressant drugs should be reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies have been conducted with fentanyl. Reproduction studies in rats revealed a significant decrease in the pregnancy rate of all experimental groups. This decrease was most pronounced in the high dosed group (1.25 mg/kg–12.5X human dose) in which one of twenty animals became pregnant.

Pregnancy: Teratogenic Effects, Pregnancy Category C

Fentanyl citrate has been shown to impair fertility and to have an embryocidal effect in rats when given in doses 0.3 times the upper human dose for a period of 12 days. No evidence of teratogenic effects have been observed after administration of fentanyl citrate to rats. There are no adequate and well-controlled studies in pregnant women. Fentanyl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

There are insufficient data to support the use of fentanyl in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fentanyl citrate is administered to a nursing woman.

Pediatric Use

The safety and efficacy of fentanyl citrate in pediatric patients under two years of age has not been established.

Rare cases of unexplained clinically significant methemoglobinemia have been reported in premature neonates undergoing emergency anesthesia and surgery which included combined use of fentanyl, pancuronium and atropine. A direct cause and effect relationship between the combined use of these drugs and the reported cases of methemoglobinemia has not been established.

ADVERSE REACTIONS

As with other narcotic analgesics, the most common serious adverse reactions reported to occur with fentanyl are respiratory depression, apnea, rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, diaphoresis, pruritus, urticaria, laryngospasm, and anaphylaxis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as droperidol is used with fentanyl, the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of droperidol.

DRUG ABUSE AND DEPENDENCE

Fentanyl Citrate Injection, USP is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Manifestations

The manifestations of fentanyl citrate overdosage are an extension of its pharmacologic actions (see CLINICAL PHARMACOLOGY) as with other opioid analgesics. The intravenous LD_{50} of fentanyl citrate is 3 mg/kg in rats, 1 mg/kg in cats, 14 mg/kg in dogs and 0.03 mg/kg in monkeys.

Treatment

In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl citrate may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

DOSAGE AND ADMINISTRATION

50 mcg = 0.05 mg = 1 mL

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used and the surgical procedure involved. Dosage should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

I. Premedication -Premedication (to be appropriately modified in the elderly, debilitated and those who have received other depressant drugs) - 50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 mL) may be administered intramuscularly 30 to 60 minutes prior to surgery.

II. Adjunct to General Anesthesia - See Dosage Range Chart

III. Adjunct to Regional Anesthesia - 50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 mL) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. Postoperatively (recovery room) - 50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 mL) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usage in children: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 2 to 3 mcg/kg is recommended.

DOSAGE RANGE CHART TOTAL DOSAGE (expressed as fentanyl base)
Low Dose - 2 mcg/kg (0.002 mg/kg) (0.04 mL/kg). Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period.
Moderate Dose - 2 to 20 mcg/kg (0.002 to 0.02 mg/kg) (0.04 to 0.4 mL/kg). Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary and careful observation of ventilation postoperatively is essential.

III. Adjunct to Regional Anesthesia - 50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 mL) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. Postoperatively (recovery room) - 50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 mL) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usage in children: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 2 to 3 mcg/kg is recommended.

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Low Dose - 2 mcg/kg (0.002 mg/kg) (0.04 mL/kg). Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period.
Moderate Dose - 2 to 20 mcg/kg (0.002 to 0.02 mg/kg) (0.04 to 0.4 mL/kg). Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary and careful observation of ventilation postoperatively is essential.
High Dose - 20 to 50 mcg/kg (0.02 to 0.05 mg/kg) (0.4 to 1 mL/kg). During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20 to 50 mcg/kg (0.02 to 0.05 mg) (0.4 to 1 mL) of fentanyl with nitrous oxide/oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH and prolactin. When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression. The main objective of this technique would be to produce "stress free" anesthesia.

DOSAGE RANGE CHART MAINTENANCE DOSE (expressed as fentanyl base)
Low Dose - 2 mcg/kg (0.002 mg/kg) (0.04 mL/kg). Additional dosages of fentanyl are infrequently needed in these minor procedures.
Moderate Dose - 2 to 20 mcg/kg (0.002 to 0.02 mg/kg) (0.04 to 0.4 mL/kg). 25 to 100 mcg (0.025 to 0.1 mg) (0.5 to 2 mL) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.
High Dose - 20 to 50 mcg/kg (0.02 to 0.05 mg/kg) (0.4 to 1 mL/kg). Maintenance dosage (ranging from 25 mcg (0.025 mg) (0.5 mL) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic

When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg/kg (0.05 to 0.1 mg/kg) (1 to 2 mL/kg) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg/kg (0.15 mg/kg) (3 mL/kg) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See **WARNINGS** and **PRECAUTIONS** for use of fentanyl citrate with other CNS depressants, and in patients with altered response.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Fentanyl Citrate Injection, USP, contains Fentanyl Citrate, USP equivalent to 50 mcg (0.05 mg) fentanyl base per mL, and is available as follows:

NDC 0209-3650-20—20 mL vial, individually packaged
NDC 0209-3660-20—50 mL vial, individually packaged

PROTECT FROM LIGHT: Retain in carton until time of use. STORE UPRIGHT.
STORE AT CONTROLLED ROOM TEMPERATURE 15° - 30° C (59° - 86° F).

CAUTION: Federal law prohibits dispensing without prescription.

Marsam Pharmaceuticals Inc.
Cherry Hill, NJ 08034

Issued 1-97 C3100

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74917

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 74-917

3. NAME AND ADDRESS OF APPLICANT
Marsam Pharmaceuticals, Inc.
Attention: Steven Brown, R.H.
Bldg. 31, 24 Olney Avenue
P.O. Box 1022
Cherry Hill, NJ 08034

4. PATENT EXCLUSIVITY
The firm states that in accordance with 314.94 there is no unexpired patent applicable to the product nor is the product entitled to a period of market exclusivity.

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Fentanyl Citrate

9. AMENDMENTS AND OTHER DATES:

Orig Submission	6/26/96
New correspondence	8/5/96
Ack. rec. ltr.	8/6/96
Amendment	1/14/97
Amendment	2/12/97
Amendment	7/25/97

10. PHARMACOLOGICAL CATEGORY
Narcotic analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Injection

14. POTENCY
50 mcg/mL

15. CHEMICAL NAME AND STRUCTURE
N-(1-phenethyl-4-piperidyl) propionanilide citrate (1:1)
Drug substance and drug product are compendial articles.

17. COMMENTS
Chemistry complete. ~~Micro def needs to be submitted to firm.~~

18. CONCLUSIONS AND RECOMMENDATIONS
~~Not approvable. CGMP violations. EER pending.~~
Approvable

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
5/16/97; 9/2/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74917

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD-640
Microbiologist's Review #2
July 31, 1997

A. 1. **ANDA** 74-917

APPLICANT Marsam

2. PRODUCT NAMES: **Fentanyl Citrate Injection USP**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 20 mL and 50 mL Vials, Intramuscular or Intravenous*

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Narcotic Analgesic

B. 1. DATE OF INITIAL SUBMISSION: June 26, 1996
(Received, June 28, 1996)

2. DATE OF AMENDMENT: July 25, 1997
Subject of this Review (Received, July 28, 1997)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: 7/31/97

C. REMARKS: The amendment provides for the response to the Microbiology Deficiencies in the Minor Amendment letter dated June 9, 1997. *The applicant stated that the ampul product contained in the original submission was withdrawn on January 14, 1997.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".

7/31/97

Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\74-917a
Initialed by F. Fang or F. Holcombe, Jr.

7/31/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74917

BIOEQUIVALENCE REVIEW(S)

SEP 30 1996

Fentanyl Citrate Injection
50 μg base/mL
2,5,10, and 20 mL Ampoules
20 and 50 mL Vials
ANDA #74917
Reviewer: Kuldeep R. Dhariwal
File name: 74917W.696

Marsam Pharmaceuticals Inc.
Building 31, Olney Ave.
P.O.Box 1022
Cherry Hill
New Jersey 08034
Submission Date:
June 26, 1996

Review of a Waiver Request

Introduction:

Fentanyl citrate injection is a potent narcotic analgesic. The reference listed drug is Sublimaze® injection by Janssen Pharmaceutica. It is available as 50 μg/mL of fentanyl base in 2 mL, 5 mL, 10 mL, and 20 mL ampoules. Sublimaze® is a sterile, non-pyrogenic, preservative free aqueous solution for intravenous or intramuscular injection.

Background:

The firm requests a waiver for evidence of bioavailability for its test product fentanyl citrate injection, 50 μg base/mL under 21 CFR 320.22(b)(1).

Formulation:

Ingredients	Test	Reference
Fentanyl citrate, USP	50 μg/mL*	50 μg/mL*
Sodium Hydroxide	to adjust pH 4.0-7.5	to adjust pH 4.0-7.5
Water for injection	q.s. 1 mL	q.s. 1 mL

* Fentanyl citrate equivalent to 50 μg/mL fentanyl base

Comments:

1. The route of administration and dosage form are the same for test and reference drug products.

2. The active and inactive ingredients are qualitatively and quantitatively the same in test and reference drug products.

3. The firm intends to package the product in 2, 5, 10, and 20 mL ampoules as well as in 20 mL and 50 mL vials. The reference listed drug Sublimaze® is available only in ampoules. However, another generic fentanyl citrate injection from Elkins-Sinn is available in ampoules as well as in 30 mL and 50 mL vials.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Marsam Pharmaceuticals demonstrates that fentanyl citrate injection 50 μg base/mL falls under 21 CFR section 320.22 (b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for the test product fentanyl citrate injection 50 μg base/mL is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Sublimaze® injection 50 μg base/mL manufactured by Janssen Pharmaceutica.

9/30/96
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR _____ Date 9/30/96

Concur: _____ Date 9/30/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA #74917 (original, duplicate), Dhariwal, HFD-655 (Nerurkar), Drug File, Division File
Draft: 092096; Final: 093096

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74917

ADMINISTRATIVE DOCUMENTS

Signed

DIVISION REVIEW SUMMARY

ANDA: 74-917

FIRM: Marsam Pharmaceuticals, Inc.
Bldg. 31, 24 Olney Avenue
P.O. Box 1022
Cherry Hill, NJ 08034

DOSAGE FORM: Injection STRENGTH: 50 mcg/mL
(20 mL and 50 mL SD vials)

DRUG: Fentanyl Citrate USP

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 1/21/98

BIO STUDY INFORMATION: Bio-waiver granted. See letter dated 10/3/96.

METHODS VALIDATION: N/A; Drug substance and drug product are articles of the USP.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? yes

The firm submitted accelerated stability data for the product packaged in both container sizes.

The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are indicated in the following table:

TEST	SPECIFICATION
Description	
pH	
Assay	
Related Compounds	
Particulate Matter	
Bacterial Endotoxins	
Sterility	

LABELING: Acceptable; See review dated 7/31/97.

STERILIZATION VALIDATION: Acceptable; See review dated 7/31/97.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?)

No information on bio-batch since a waiver was granted.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

See below.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The firm manufactured a batch to support the intended production batch size of for the 20 mL vial.

The firm manufactured a batch to support the intended production batch size of for the 50 mL vial.

RECOMMENDATION: APPROVABLE

SIGNATURE: DATE: 9/2/97

The finished product tests and specifications are as follows:

TEST	SPECIFICATION
Description	
Identification	
pH	
Volume	
Assay	
Related Compounds	
Particulate Matter	
Bacterial Endotoxins	
Sterility	
Confirmation sample*	conforms

*performed on commercial batches

Component	amt/mL
Fentanyl Citrate USP	
Water for Injection USP	
Sodium Hydroxide NF 1N solution	
Nitrogen NF	

*Used only to provide pressure in
**Equivalent to 50 mcg/mL of fentanyl base

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74917

CORRESPONDENCE

MARSAM
PHARMACEUTICALS INC.

January 14, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AA

Subject: **AMENDMENT**
ANDA 74-917, Fentanyl Citrate Injection, USP 50 mcg/mL
2 mL, 5 mL, 10 mL and 20 mL Ampuls
20 mL and 50 mL Vials

Dear Sir/Madam:

In accordance with 21 CFR 314.96(a) we are submitting an amendment to the Abbreviated New Drug Application for the above referenced product to provide for the withdrawal of the 2 mL, 5 mL, 10 mL and 20 mL ampuls from the application.

We will continue to seek approval of the above referenced application for the 20 mL and 50 mL vial sizes. Prior to submission of final printed labeling, the "How Supplied" section of the package insert will be revised to delete reference to the ampuls.

The decision to withdraw the 2 mL, 5 mL, 10 mL and 20 mL ampuls is without prejudice to refiling at a later date.

In accordance with 21 CFR 314.96 (b), we hereby certify that a true and complete copy of this amendment is being submitted to our home FDA district office (New Jersey District Office, North Brunswick Resident Post).

Should you have any questions or comments regarding this submission, please do not hesitate to contact Nilda Ramos at (609) 489-5323.

Sincerely,

Thomas L. Pituk

Thomas L. Pituk
Director, Regulatory Affairs

Enclosures
cc: FDA New Jersey District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902

RECEIVED
JAN 15 1997
GENERIC DRUGS

Building 31, Olney Ave. P.O. Box 1022 Cherry Hill, New Jersey 08034, (609) 424-5600
Telex: 5106012909 Marsam Pharma UQ
Facsimile: 609-751-8784

MARSAM
PHARMACEUTICALS INC.

NEW CORRESP
NC

August 5, 1996

RECEIVED
AUG 0 9 1996
GENERIC DRUGS

Anna Marie Weikel, CSO
Office of Generic Drugs FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Subject: New ANDA 74917
Fentanyl Citrate Injection, USP
2, 5, 10 and 20 mL Ampuls, 20 and 50 mL Vials

Dear Ms. Weikel:

Pursuant to your request, I sent by facsimile a cover letter with an executed copy of the Environmental Impact Analysis Statement on July 30, 1996. Enclosed is the hard copy of the same.

If you have any questions, please feel free to contact me at (609) 424-5600, Ext. 319.

Sincerely,

Nandan Mavinkurve
Manager, Regulatory Affairs

Enclosure(s)

8596fda/nm

8-16-96

UPS 06467350110

Building 31, Olney Ave. P.O. Box 1022 Cherry Hill, New Jersey 08034, (609) 424-5600
Telex: 5106012909 Marsam Pharma UQ
Facsimile: 609-751-8784

MARSAM
PHARMACEUTICALS INC.

505(j)(2)(a) info acceptable for filing. Carol Marie N. Weikel

Labeling Review Completed 10/9/96

June 26, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
JUN 28 1996
GENERIC DRUGS

Subject: **NEW ANDA**
Fentanyl Citrate Injection, USP 50 mcg/mL
2, 5, 10 and 20 mL Ampuls
20 mL and 50 mL Vials

Dear Sir/Madam:

In accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act, we are submitting the attached Abbreviated New Drug Application (ANDA) for the above referenced product. The listed drug upon which this application is based is Sublimaze® (fentanyl citrate) Injection by Janssen Pharmaceutica. Draft labeling is included (Section V) which is based on current approved labeling for Sublimaze® (ampuls) and for Elkins-Sinn, Inc. Fentanyl Citrate Injection, USP (vials).

This submission consists of three (3) volumes. As required, archival and review copies are provided, and a true copy of the ANDA is being sent concurrently to our home district FDA office. (Please refer to Section XXI for the District Copy Certification and Debarment Certification.) To facilitate the microbiological review, pertinent information has been placed in Section XI.2 of the ANDA. A request for waiver of bioequivalence testing is located in Section VI.1.

Included in Section XVII are stability data for the product in 2 mL, 5 mL, 10 mL and 20 mL ampuls, and in 20 mL vials and 50 mL vials. Based on these data, we are requesting a 24 month expiration date for this product.

Building 31, Olney Ave. P.O. Box 1022 Cherry Hill, New Jersey 08034, (609) 424-5600
Telex: 5106012909 Marsam Pharma UQ
Facsimile: 609-751-8784

MARSAM
PHARMACEUTICALS INC.

During the course of your review of this application, if you have questions or comments which can be addressed via telephone and/or telefax, please do not hesitate to contact the following:

Primary Contact
Nilda Ramos
Phone: (609) 424-5600, Ext. 323
Fax: (609) 751-8784

Alternate Contact
Nandan Mavinkurve
Phone: (609) 424-5600, Ext. 319
Fax: (609) 751-8784

Sincerely,

Thomas L. Pituk

Thomas L. Pituk
Director, Regulatory Affairs

Enclosures
cc: FDA Newark District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902

noted
ps 7/31/97

MARSAM
PHARMACEUTICALS INC.

July 25, 1997

AMENDMENT
N/Am

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Subject: **MINOR AMENDMENT: RESPONSE TO MICROBIOLOGY DEFICIENCIES.**
AADA 74-917, Fentanyl Citrate Injection, 50 mcg/mL

Dear Sir or Madam:

This Minor Amendment to the subject Application is submitted in response to the letter dated June 9, 1997 from the Office of Generic Drugs.

We have restated each Microbiology Deficiency, followed by our response to the same. We have revised the container labels and the package insert in accordance with the points listed under Labeling Deficiencies. Twelve copies of the final printed labeling along with a side-by-side comparison of the proposed labeling are included in this Amendment. Certain additional chemistry, manufacturing and controls changes (other than those made in response to the deficiency letter) are summarized in the section entitled "Additional Information". Documents revised to reflect the changes described are also included in that section.

We certify that a true copy of the sections of this Amendment relating to the chemistry, manufacturing and controls has been submitted to our home district office (New Jersey District), in accordance with 21 CFR 314.96(b).

We have responded fully to all FDA questions regarding this Application. If any minor issues arise during the review of this response, we would appreciate their resolution by telephone or facsmile. For this purpose, please contact Nandan Mavinkurve at (609) 489-5319 (telephone) or at (609) 424-9418 (facsimile).

RECEIVED
JUL 28 1997
GENERIC DRUGS

Sincerely,

Steven W. Brown, R.Ph
Director, Regulatory Affairs

7-30-97

Building 31, Olney Ave. P.O. Box 1022 Cherry Hill, New Jersey 08034, (609) 424-5600
Telex: 5106012909 Marsam Pharma UQ
Facsimile: 609-751-8784

MARSAM
PHARMACEUTICALS INC.

February 12, 1997

AMENDMENT
N AC

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Subject: **MAJOR AMENDMENT**
ANDA 74-917, Fentanyl Citrate Injection, USP, 50 mcg/mL
20 mL and 50 mL Vials

Dear Sir/Madam:

In response to your not approvable letter dated December 11, 1996, we are submitting this amendment to the Abbreviated New Drug Application for the above referenced product.

Please note that an amendment was submitted to this application on January 14, 1997 to provide for the withdrawal of the 2 mL, 5 mL, 10 mL and 20 mL ampuls without prejudice to refiling at a later date. Our response to your above referenced not approvable letter is intended to address the deficiency items which apply to the 20 mL and 50 mL vial sizes, for which we will continue to seek approval. For each deficiency item, we have restated each comment (in bold) followed by our response and any necessary attachments.

Additional CMC changes (other than those made in response to the not approvable letter) for the referenced product are listed in the CMC Changes section provided. Revised documents are included in this section. Many of the observations by the district office during the pre-approval inspection for the referenced product were for items which are covered in your not approvable letter, and which we have addressed in our response. CMC changes made in response to observations during the pre-approval inspection, which are not covered in your not approvable letter, are included in the CMC Changes section of this amendment.

In accordance with 21 CFR 314.96 (b), we hereby certify that a true and complete copy of this amendment is being submitted to our home FDA district office (New Jersey District Office, North Brunswick Resident Post).

Should you have any questions or comments regarding this submission, please do not hesitate to contact Nilda Ramos at (609) 489-5323.

Sincerely,

Thomas L. Pituk

Thomas L. Pituk
Director, Regulatory Affairs

RECEIVED
FEB 13 1997
GENERIC DRUGS

Enclosures
cc: FDA New Jersey District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902

Building 31, Olney Ave. P.O. Box 1022 Cherry Hill, New Jersey 08034, (609) 424-5600
Telex: 5106012909 Marsam Pharma UQ
Facsimile: 609-751-8784

ANDA 74-917

Marsam Pharmaceuticals, Inc.
Attention: Thomas L. Pituk
Building 31, Olney Ave.
P.O. Box 1022
Cherry Hill, NJ 08034

AUG 6 1996

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Fentanyl Citrate Injection, USP 50 mcg/mL, 2 mL, 5mL, 10 mL, and 20 mL Ampuls; 20 mL and 50 mL Vials

DATE OF APPLICATION: June 26, 1996

DATE OF RECEIPT: June 28, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ms. Kassandra Sherrod
Project Manager
(301) 594-1300

Sincerely yours,

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-917
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSB 8/6/96 date
HFD-615/AMWeikel, CSO 7/31/96 date
HFD-645/BArnwine, Sup. Chem. _____ date
X:\new\firmsam\marsam\74917.ack
F/T bcw/7-31-96
ANDA Acknowledgement Letter