CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75170

APPROVAL LETTER

ANDA 75-170

SEP 28 1998

Faulding Pharmaceutical Co.
Attention: Heike Maaser, Ph.D.
200 Elmora Avenue
Elizabeth, New Jersey 07207

Dear Madam:

This is in reference to your abbreviated new drug application dated July 22, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Butorphanol Tartrate Injection USP, (Preservative-Free) 1 mg/mL and 2 mg/mL.

Reference is also made to your amendments dated March 20, June 18, and July 24, 1998.

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 Butorphanol Tartrate Injection USP, (Preservative-Free) 1 mg/mL and 2 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Stadol® Injection (Preservative Free), 1 mg/mL and 2 mg/mL, of Apothecon, 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 and 314.98. 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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

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

9-28-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75170

DRAFT FINAL PRINTED LABELING

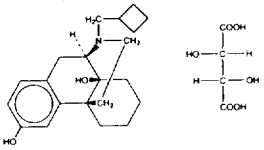
BUTORPHANOL TARTRATE INJECTION, USP

Faulding

SAMPLE

DESCRIPTION

Butorphanol tartrate is a synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. The chemical name is (-)-17-(cyclobutylmethyl)morphinan-3,14-diol,D-(-)-tartrate(1:1)(salt). The molecular formula is $C_{21}H_{29}NO_2 \cdot C_4H_6O_6$, which corresponds to a molecular weight of 477.56 and the following structural formula:



Butorphanol tartrate is a white powder. Its solutions are slightly acidic. It melts between 102.8°C (217°F) and 103.9°C (219°F), with decomposition. It is sparingly soluble in water; slightly soluble in methanol; insoluble in alcohol and chloroform; soluble in dilute acids. The dose is expressed as the tartrate salt. One milligram of the salt is equivalent to 0.68 mg of the free base. The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5.

Butorphanol tartrate injection is a sterile, parenteral, aqueous solution of butorphanol tartrate for intravenous or intramuscular administration. Each mL of solution contains 1 or 2 mg of butorphanol tartrate. In addition, each mL contains 3.3 mg citric acid, 6.4 mg sodium citrate, and 6.4 mg sodium chloride. The pH range is 3.0 to 5.5.

CLINICAL PHARMACOLOGY

General Pharmacology and Mechanism of Action:

Butorphanol is a mixed agonist-antagonist with low intrinsic activity at receptors of the μ-opioid type (morphine-like). It is also an agonist at κ-opioid receptors.

Its interactions with these receptors in the central nervous system apparently mediate most of its pharmacologic effects, including analgesia.

In addition to analgesia, CNS effects include depression of spontaneous respiratory activity and cough, stimulation of the emetic center, miosis and sedation. Effects possibly mediated by non-CNS mechanisms include alteration in cardiovascular resistance and capacitance, bronchomotor tone, gastrointestinal secretory and motor activity and bladder sphincter activity.

In an animal model, the dose of butorphanol tartrate required to antagonize morphine analgesia by 50% was similar to that for nalorphine, less than that for pentazocine and more than that for naloxone.

The pharmacological activity of butorphanol metabolites has not been studied in humans; in animal studies, butorphanol metabolites have demonstrated some analgesic activity.

In human studies of butorphanol (see **Clinical Trials**), sedation is commonly noted at doses of 0.5 mg or more. Narcosis is produced by 10 to 12 mg doses of butorphanol administered over 10 to 15 minutes intravenously.

Butorphanol, like other mixed agonist-antagonists with a high affinity for the kappa receptor, may produce unpleasant psychotomimetic effects in some individuals.

Nausea and/or vomiting may be produced by doses of 1 mg or more administered by any route.

In human studies involving individuals without significant respiratory dysfunction, 2 mg of butorphanol IV and 10 mg of morphine sulfate IV depressed respiration to a comparable degree. At higher doses, the magnitude of respiratory depression with butorphanol is not appreciably increased; however, the duration of respiratory depression is longer. Respiratory depression noted after administration of butorphanol to humans by any route is reversed by treatment with naloxone, a specific opioid antagonist (see Treatment in **OVERDOSAGE**).

Butorphanol tartrate demonstrates antitussive effects in animals at doses less than those required for analgesia.

Hemodynamic changes noted during cardiac catheterization in patients receiving single 0.025 mg/kg intravenous doses of butorphanol have included increases in pulmonary artery pressure, wedge pressure and vascular resistance, increases in left ventricular end diastolic pressure and in systemic arterial pressure.

Pharmacodynamics:

The analgesic effect of butorphanol is influenced by the route of administration. Onset of analgesia is within a few minutes for intravenous administration, within 15 minutes for intramuscular injection.

Peak analgesic activity occurs within 30 to 60 minutes following intravenous and intramuscular administration.

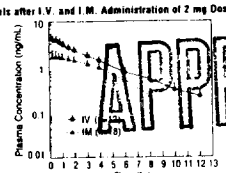
The duration of analgesia varies depending on the pain model as well as the route of administration, but is generally 3 to 4 hours with IM and IV doses as defined by the time 50% of patients required remedication. In postoperative studies, the duration of analgesia with IV or IM butorphanol was similar to morphine, meperidine and pentazocine when administered in the same fashion at equipotent doses (see **Clinical Trials**).

Pharmacokinetics:

Butorphanol tartrate is rapidly absorbed after IM injection and peak plasma levels are reached in 20 to 40 minutes.

Following its initial absorption/distribution phase, the single dose pharmacokinetics of butorphanol by the intravenous and intramuscular routes of administration are similar. (see **Figure 1**)

Figure 1 - Butorphanol Plasma Levels after I.V. and I.M. Administration of 2 mg Dose.



Serum protein binding is independent of concentration over the range achieved in clinical practice (up to 7 ng/mL) with a bound fraction of approximately 80%.

The volume of distribution of butorphanol varies from 305 to 901 liters and total body clearance from 52 to 154 liters/hr (see **Table 1**).

Table1-Mean Pharmacokinetic Parameters of Intravenous Butorphanol in Young and Elderly Subjects[a]

Parameters	Young	Elderly
AUC(inf)[b]	7.24 (1.57)[d]	8.71 (2.02)[d]
(hr·ng/mL)	(4.40-9.77)[e]	(4.76-13.03)
Half-life(hr)	4.56 (1.67)	5.61 (1.36)
	(2.06-8.70)	(3.25-8.79)
Volume of	487 (155)	552 (124)
Distribution[c](L)	(305-901)	(305-737)
Total body	99 (23)	82 (21)
Clearance(L/hr)	(70-154)	(52-143)

a) Young subjects (n=24) are from 20 to 40 years old and elderly (n=24) are greater than 65 years of age

b) Area under plasma concentration-time curve after a 1 mg dose

c) Derived from IV data

d) Mean (1 S.D.)

e) (range of observed values)

The drug is transported across the blood-brain and placental barriers and into human milk (see Labor and Delivery, and Nursing Mothers under **PRECAUTIONS**).

Butorphanol is extensively metabolized in the liver. Metabolism is qualitatively and quantitatively similar following intravenous or intramuscular administration. Oral bioavailability is only 5 to 17% because of extensive first pass metabolism of butorphanol.

The major metabolite of butorphanol is hydroxybutorphanol, while norbutorphanol is produced in small amounts. Both have been detected in plasma following administration of butorphanol, with norbutorphanol present at trace levels at most time points. The elimination half life of hydroxybutorphanol is about 18 hours and as a consequence considerable accumulation occurs when butorphanol is dosed to steady state.

Elimination occurs by urine and fecal excretion. When ^{3}H labeled butorphanol is administered to normal subjects, most (70 to 80%) of the dose is recovered in the urine, while approximately 15% is recovered in the feces.

About 5% of the dose is recovered in the urine as butorphanol. Forty-nine percent is eliminated in the urine as hydroxybutorphanol. Less than 5% is excreted in the urine as norbutorphanol (see also **CLINICAL PHARMACOLOGY** above).

Butorphanol pharmacokinetics in the elderly differ from younger patients (see **Table 1**).

In renally impaired patients with creatinine clearances < 30 mL/min the elimination half-life is approximately doubled and the total body clearance is approximately one-half (10.5 hours [clearance 150 L/h] as compared to 5.8 hours [clearance 260 L/h] in normals). No effect was observed on Cmax or Tmax after a single dose.

For further recommendations refer to statements on use in Geriatric Patients, Hepatic Disease, Renal Disease, and statement on Drug Interactions in the **PRECAUTIONS** section and Individualization of Dosage, below).

Clinical Trials:
The effectiveness of opioid analgesics varies in different pain syndromes. Studies with butorphanol tartrate injection have been performed in postoperative (primarily abdominal and orthopedic) pain and pain during labor and delivery, as preoperative and preanesthetic medication, and as a supplement to balanced anesthesia (see below).

Use in the Management of Pain:
Postoperative Pain:
The analgesic efficacy of butorphanol tartrate injection in postoperative pain was investigated in several double-blind active-controlled studies involving 958 butorphanol-treated patients. The following doses were found to have approximately equivalent analgesic effect: 2 mg butorphanol, 10 mg morphine, 40 mg pentazocine, and 80 mg meperidine.

After intravenous administration of butorphanol tartrate, onset and peak analgesic effect occurred by the time of the first observation (30 minutes). After intramuscular administration, pain relief onset occurred at 30 minutes or less, and peak effect occurred between 30 minutes and one hour. The duration of action of butorphanol tartrate injection was 3 to 4 hours when defined as the time necessary for pain intensity to return to pretreatment level or the time to retreatment.

Preanesthetic Medication:
Butorphanol tartrate injection (2 mg and 4 mg) and meperidine (80 mg) were studied for use as preanesthetic medication in hospitalized surgical patients. Patients received a single intramuscular dose of either butorphanol or meperidine approximately 90 minutes prior to anesthesia. The anesthesia regimen included barbiturate induction, followed by nitrous oxide and oxygen with halothane or enflurane, with or without a muscle relaxant.

Anesthetic preparation was rated as satisfactory in all 42 butorphanol patients regardless of the type of surgery.

Balanced Anesthesia:
Butorphanol tartrate administered intravenously (mean dose 2 mg) was compared to intravenous morphine sulfate (mean dose 10 mg) as premedication shortly before thiopental induction, followed by balanced anesthesia in 50 ASA Class 1 and 2 patients. Anesthesia was then maintained by repeated intravenous doses, averaging 4.6 mg butorphanol tartrate and 22.8 mg morphine per patient.

Anesthetic induction and maintenance were generally rated as satisfactory with both butorphanol (25 patients) and morphine (25 patients) regardless of the type of surgery performed. Emergence from anesthesia was comparable with both agents.

Labor (see PRECAUTIONS):
The analgesic efficacy of intravenous butorphanol tartrate injection was studied in pain during labor. In a total of 145 patients butorphanol tartrate (1 mg and 2 mg) was as effective as 40 mg and 80 mg of meperidine (144 patients) in the relief of pain in labor with no effect on the duration or progress of labor. Both drugs readily crossed the placenta and entered fetal circulation. The condition of the infants in these studies, determined by Apgar scores at 1 and 5 minutes (8 or above) and time to sustained respiration, showed that butorphanol had the same effects on the infants as meperidine.

In these studies neurobehavioral testing in infants exposed to butorphanol tartrate injection at a mean of 18.6 hours after delivery, showed no significant differences between treatment groups.

Individualization of Dosage:
Use of butorphanol in geriatric patients, patients with renal impairment, patients with hepatic impairment, and during labor requires extra caution (see below and appropriate sections in **PRECAUTIONS**).

For pain relief the recommended initial dosage regimen of butorphanol tartrate injection is 1 mg IV or 2 mg IM with repeated doses every 3 to 4 hours, as necessary. This dosage regimen is likely to be effective for the majority of patients. Dosage adjustments of butorphanol should be based on observations of its beneficial and adverse effects. The initial dose in the elderly and in patients with renal or hepatic impairment should generally be half the recommended adult dose (0.5 mg IV and 1 mg IM). Repeat doses in these patients should be determined by the patient's response rather than at fixed intervals but will generally be no less than 6 hours (see **PRECAUTIONS**).

The usual preoperative dose is 2 mg IM given 60 to 90 minutes before surgery or 2 mg IV shortly before induction. This is approximately equivalent in sedative effect to 10 mg morphine or 80 mg meperidine. This single preoperative dose should be individualized based on age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used and the surgical procedure involved.

During maintenance in balanced anesthesia the usual incremental dose of butorphanol tartrate is 0.5 mg to 1 mg IV. The incremental dose may be higher, up to 0.06 mg/kg (4 mg/70 kg), depending on previous sedative, analgesic and hypnotic drugs administered. The total dose of butorphanol will vary; however, patients seldom require less than 4 mg or more than 12.5 mg (approximately 0.06 to 0.18 mg/kg).

As with other opioids of this class, butorphanol may not provide adequate intraoperative analgesia in every patient or under all conditions. A failure to achieve successful analgesia during balanced anesthesia is commonly reflected by increases in general sympathetic tone. Consequently, if blood pressure or heart rate continue to rise, consideration should be given to adding a potent volatile liquid inhalation anesthetic or another intravenous medication.

In labor, the recommended initial dose of butorphanol tartrate is 1 mg or 2 mg IM or IV in mothers with fetuses of 37 weeks gestation or beyond and without signs of fetal distress. Dosage adjustments of butorphanol in labor should be based on initial response with consideration given to concomitant analgesic or sedative drugs and the expected time of delivery. A dose should not be repeated in less than four hours nor administered less than four hours prior to anticipated delivery (see **PRECAUTIONS**).

INDICATIONS AND USAGE
Butorphanol tartrate injection is indicated for the management of pain when the use of an opioid analgesic is appropriate.

Butorphanol tartrate injection is also indicated as preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of pain during labor.

CONTRAINDICATIONS
Butorphanol tartrate injection is contraindicated in patients hypersensitive to butorphanol tartrate.

WARNINGS
Patients Dependent on Narcotics:
Because of its opioid antagonist properties, butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness and diarrhea.

Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

Drug Abuse:
All routes of administration of butorphanol have been associated with episodes of abuse, with most reports involving outpatient treatment of chronically painful conditions. Of the cases received there were more reports of abuse with the nasal spray formulation than with the formulation administered parenterally. In general, patients receiving opioid treatment for an extended period of time are at a higher risk for abuse.

Drug Dependence, Tolerance and Withdrawal:
Prolonged use of butorphanol tartrate for the treatment of chronically painful conditions may also result in dependence. The development of dependence may be marked by tolerance (a decrease in response to a given dose) which may lead to non-medical escalation and craving, or drug seeking behavior. Abrupt cessation of use by dependent patients may result in symptoms of withdrawal.

Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and dependence. (See **DRUG ABUSE AND DEPENDENCE** section below).

PRECAUTIONS
Head Injury and Increased Intracranial Pressure:
As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control:
Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease:
In patients with severe hepatic or renal disease the initial dosage interval for butorphanol should be increased to 6 to 8

hours until the response has been well characterized. Subsequent doses should be determined by patient response rather than being scheduled at fixed intervals (see **CLINICAL PHARMACOLOGY, Individualization of Dosage**).

Cardiovascular Effects:
Because butorphanol may increase the work of the heart, especially the pulmonary circuit (see **CLINICAL PHARMACOLGY**), the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

Use in Ambulatory Patients:
1. Opioid analgesics, including butorphanol, impair the mental and physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Effects such as drowsiness or dizziness can appear, usually within the first hour after dosing. These effects may persist for varying periods of time after dosing. Patients who have taken butorphanol should not drive or operate dangerous machinery for at least 1 hour and until the effects of the drug are no longer present.
2. Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with drugs that affect the central nervous system (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects such as drowsiness, dizziness and impaired mental function.
3. This is one of a class of drugs known to be abused and thus should be handled accordingly.

Drug Interactions:
Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.

It is not known if the effects of butorphanol are altered by concomitant medications that affect hepatic metabolism of drugs (erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

No information is available about the use of butorphanol concurrently with MAO inhibitors.

Information for Patients:
See **PRECAUTIONS, Use in Ambulatory Patients**.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Two year carcinogenicity studies were conducted in mice and rats given butorphanol tartrate in the diet up to 60 mg/kg/day (180 mg/m^2 for mice and 354 mg/m^2 for rats). There was no evidence of carcinogenicity in either species in these studies.

Butorphanol was not genotoxic in *S. typhimurium* or *E. coli* assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.

Rats treated orally with 160 mg/kg/day (944 mg/m^2) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/m^2) subcutaneous dose.

Pregnancy:
Pregnancy Category C
Reproduction studies in mice, rats and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. However, pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/m^2) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (5.1 mg/m^2) and 60 mg/kg/oral (10.2 mg/m^2) also showed higher incidences of post-implantation loss in rabbits.

There are no adequate and well-controlled studies of butorphanol in pregnant women before 37 weeks of gestation. Butorphanol tartrate injection should be used during pregnancy only if the potential benefit justifies the potential risk to the infant.

Labor and Delivery:
There have been rare reports of infant respiratory distress/apnea following the administration of butorphanol during labor. The reports of respiratory distress/apnea have been associated with administration of a dose within two hours of delivery, use of multiple doses, use with additional analgesic or sedative drugs, or use in preterm pregnancies. (See **OVERDOSAGE, Treatment**)

In a study of 119 patients, the intravenous administration of 1 mg butorphanol tartrate during labor was associated with transient (10 to 90 minutes) sinusoidal fetal heart rate patterns, but was not associated with adverse neonatal outcomes. In the presence of an abnormal fetal heart rate pattern, butorphanol should be used with caution.

Nursing Mothers:
Butorphanol has been detected in milk following administration of butorphanol tartrate injection to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 microgram/liter of milk in a mother receiving 2 mg IM four times a day).

Pediatric Use:
Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

Geriatric Use:
The initial dose of butorphanol recommended for elderly patients is half the usual dose at twice the usual interval. Subsequent doses and intervals should be based on the patient response (see **CLINICAL PHARMACOLOGY**, Individualization of Dosage).

Due to changes in clearance, the mean half-life of butorphanol is increased by 25% in patients over the age of 65. Elderly patients may be more sensitive to its side effects.

ADVERSE REACTIONS
A total of 2,446 patients were studied in butorphanol clinical trials. Approximately half received butorphanol tartrate injection with the remainder receiving butorphanol tartrate nasal spray. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.

The adverse experiences described below are based on data from short- and long-term clinical trials as well as postmarketing experience in patients receiving butorphanol tartrate injection. There has been no attempt to correct for placebo effect or subtract the frequencies reported by placebo treated patients in controlled trials.

The most frequently reported adverse experiences across all clinical trials with butorphanol tartrate injection and nasal spray were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with the nasal spray only, nasal congestion (13%) and insomnia (11%) were frequently reported.

The following adverse experiences were reported at a frequency of 1% or greater, and were considered to be probably related to the use of butorphanol:

Body as a whole: asthenia/lethargy*, headache*, sensation of heat.

Cardiovascular: VASODILATION*, PALPITATIONS.

Digestive: ANOREXIA*, CONSTIPATION*, dry mouth*, nausea and/or vomiting (13%), stomach pain.

Nervous: anxiety, confusion*, dizziness (19%), euphoria, floating feeling, INSOMNIA (11%), nervousness, paresthesia, somnolence (43%), TREMOR, DRUG DEPENDENCE* or WITHDRAWAL SYNDROME*, (see **DRUG ABUSE AND DEPENDENCE**).

Respiratory: BRONCHITIS, COUGH, DYSPNEA*, EPISTAXIS*, NASAL CONGESTION (13%), NASAL IRRITATION*, PHARYNGITIS*, RHINITIS*, SINUS CONGESTION*, SINUSITIS, UPPER RESPIRATORY INFECTION*.

Skin and appendages: sweating/clammy*, pruritus.

Special senses: blurred vision, EAR PAIN, TINNITUS*, UNPLEASANT TASTE* (also seen in short-term trials with butorphanol tartrate nasal spray).

(Reactions occuring with a frequency of 3 to 9% are marked with an asterisk (*). Reactions reported predominantly from long-term trials with butorphanol tartrate nasal spray are CAPITALIZED.)

The following adverse experiences were reported from postmarketing experience or with a frequency of less than 1% in clinical trials, and were considered to be probably related to the use of butorphanol:

Body as a Whole: *excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements.*

Cardiovascular: hypotension, syncope.

Nervous: abnormal dreams, agitation, dysphoria, *excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements*, hallucinations, hostility, *vertigo*.

Skin and appendages: rash/hives.

Urogenital: impaired urination.

(Reactions reported only from post-marketing experience are *italicized*.)

The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term butorphanol tartrate nasal spray trials and from post-marketing experiences under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.

Cardiovascular: chest pain, hypertension, tachycardia.

Body as a whole: edema.

Cardiovascular: hypertension.

Nervous: *convulsion, delusion,* depression.

Respiratory: *apnea,* shallow breathing.

(Reactions reported only from post-marketing experience are *italicized.*)

DRUG ABUSE AND DEPENDENCE

Butorphanol tartrate injection is listed in SCHEDULE IV of the Controlled Substances Act (CSA).

Clinical Trial Experience

Some patients in clinical trials conducted in patients who were largely opiate-naive, had experiences typically associated with opioid abuse or dependence. These included rapid development of tolerance to the drug in which patients increased their dosage to higher levels than prescribed and reports of euphoria.

Withdrawal symptoms were identified in patients using butorphanol tartrate nasal spray in controlled clinical trials. Patients abruptly discontinuing butorphanol tartrate nasal spray after extended use or high doses were at greatest risk. Withdrawal symptoms included anxiety, agitation, tremulousness, diarrhea, chills, sweats, insomnia, confusion, incoordination, drug cravings and hallucinations.

Postmarketing Experience

Butorphanol tartrate has been associated with episodes of abuse and dependence. Of the cases received, there were more reports of abuse with the nasal spray formulation than with the injectable formulation.

Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and dependence with butorphanol tartrate. Special care should be exercised in administering butorphanol to patients with a history of drug abuse or to patients receiving the drug on a repeated basis for an extended period of time.

OVERDOSAGE

Clinical Manifestations:

The clinical manifestations of butorphanol overdose are those of opioid drugs in general. Consequences of overdose vary with the amount of butorphanol ingested and the degree of tolerance of the patient to the effects of opiates. The most serious symptoms are hypoventilation, cardiovascular insufficiency and/or coma.

Other symptoms of overdose may include excessive drug effect (e.g. sedation, dizziness, nausea or vomiting). This may be associated with transient difficulty speaking or executing purposeful movements. Many of the reported cases have involved people who are not tolerant to the effects of opiates and who use larger doses of butorphanol to initiate therapy (more than 2 mg butorphanol tartrate injection).

Overdose can occur due to accidental or intentional misuse of butorphanol, especially in young children who may gain access to the drug in the home.

Treatment:

The management of suspected butorphanol overdosage includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness and vital signs. Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required. An adequate intravenous portal should be maintained to facilitate treatment of hypotension associated with vasodilation.

The use of a specific opioid antagonist such as naloxone should be considered. As the duration of butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.

In managing cases of suspected butorphanol overdosage, the possibility of multiple drug ingestion should always be considered.

DOSAGE AND ADMINISTRATION

Factors to be considered in determing the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, patients with hepatic or renal disease or in labor requires extra caution (see **PRECAUTIONS** and **CLINICAL PHARMACOLOGY**, Individualization of Dosage). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

Use for Pain:

Intravenous: The usual recommended single dose for IV administration is 1 mg repeated every three to four hours as necessary. The effective dosage range, depending on the severity of pain, is 0.5 mg to 2 mg repeated every 3 to 4 hours.

Intramuscular: The usual recommended single dose for IM administration is 2 mg in patients who will be able to remain recumbent, in the event drowsiness or dizziness occurs. This may be repeated every 3 to 4 hours as necessary. The effective dosage range depending on the severity of pain is 1 mg to 4 mg repeated every 3 to 4 hours. There are insufficient clinical data to recommend single doses above 4 mg.

Use as Preoperative/Preanesthetic Medication:

The preoperative medication dosage of butorphanol should be individualized (see **CLINICAL PHARMACOLOGY**, Individualization of Dosage). The usual adult dose is 2 mg IM, administered 60 to 90 minutes before surgery. This is approximately equivalent in sedative effect to 10 mg morphine or 80 mg meperidine.

Use in Balanced Anesthesia:

The usual dose of butorphanol tartrate injection is 2 mg IV shortly before induction and/or 0.5 mg to 1 mg IV in increments during anesthesia. The increment may be higher, up to 0.06 mg/kg (4 mg/70 kg), depending on previous sedative, analgesic, and hypnotic drugs administered. The total dose of butorphanol tartrate will vary; however, patients seldom require less than 4 mg or more than 12.5 mg (approximately 0.06 mg/kg to 0.18 mg/kg).

Labor:

In patients at full term in early labor a 1 mg to 2 mg dose of butorphanol tartrate IV or IM may be administered and repeated after 4 hours. Alternative analgesia should be used for pain associated with delivery or if delivery is expected to occur within 4 hours.

If concomitant use of butorphanol with drugs that may potentiate its effects is deemed necessary (see Drug Interactions in **PRECAUTIONS** section) the lowest effective dose should be employed.

Safety and Handling:

Butorphanol tartrate injection is supplied in sealed delivery systems that have a low risk of accidental exposure to health care workers. Ordinary care should be taken to avoid aerosol generation while preparing a syringe for use. Following skin contact, rinsing with cool water is recommended.

The disposal of Schedule IV controlled substances must be consistent with State and Federal Regulations.

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

HOW SUPPLIED

Butorphanol Tartrate Injection, USP 1 mg/1 mL

Carton of ten 1 mL single dose vials (NDC 61703-317-06)

Butorphanol Tartrate Injection, USP 2 mg/1 mL

Carton of ten 1 mL single dose vials (NDC 61703-318-06)

STORAGE CONDITIONS

Store at controlled room temperature, between 15°C to 30°C (59°F to 86°F).

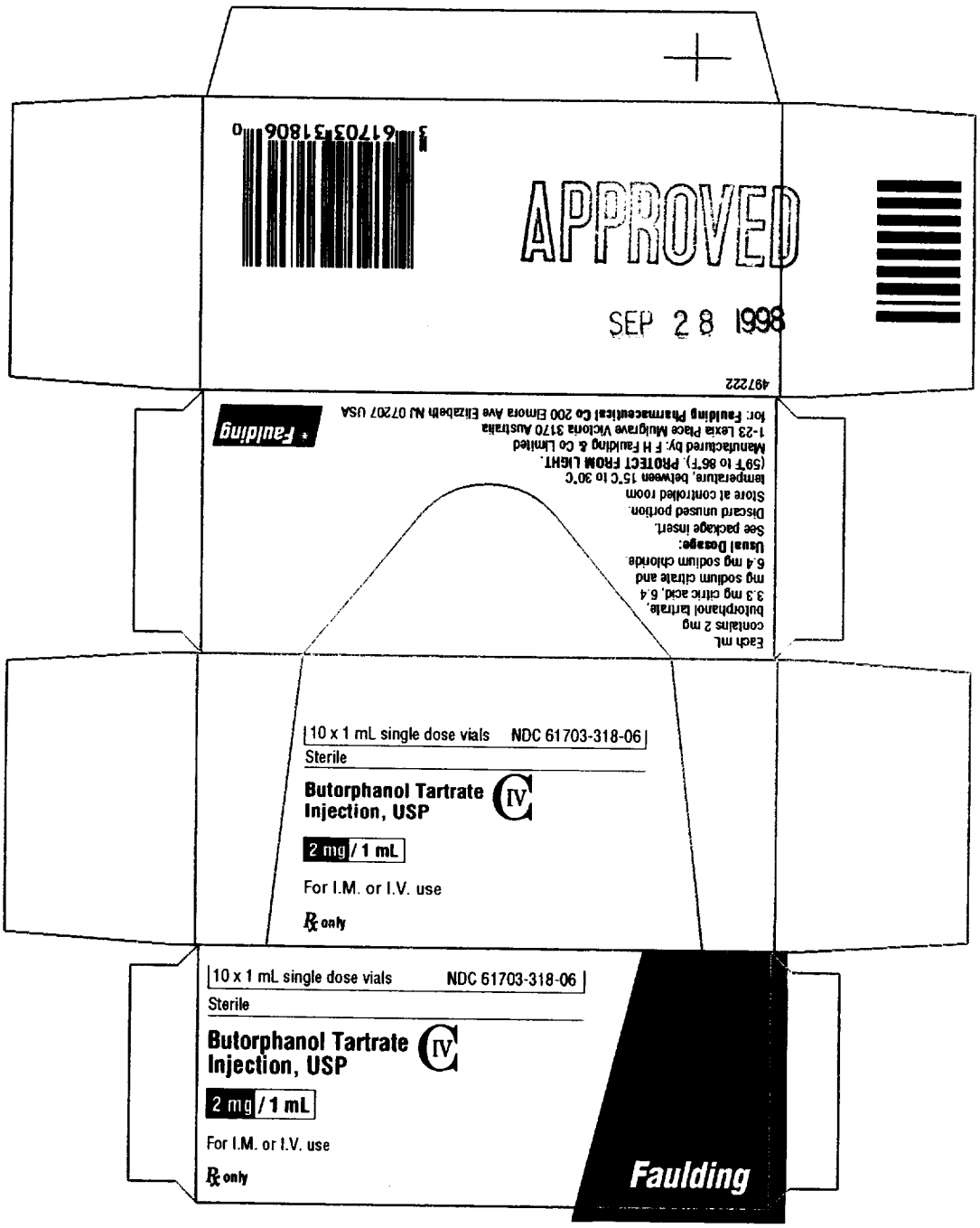
℞ **only**

Manufactured by:
F.H. Faulding & Co. Limited
1-23 Lexia Place
Mulgrave Victoria 3170 Australia
for:
Faulding Pharmaceutical Co
200 Elmora Avenue
Elizabeth NJ 07207 USA

July 1998

493313

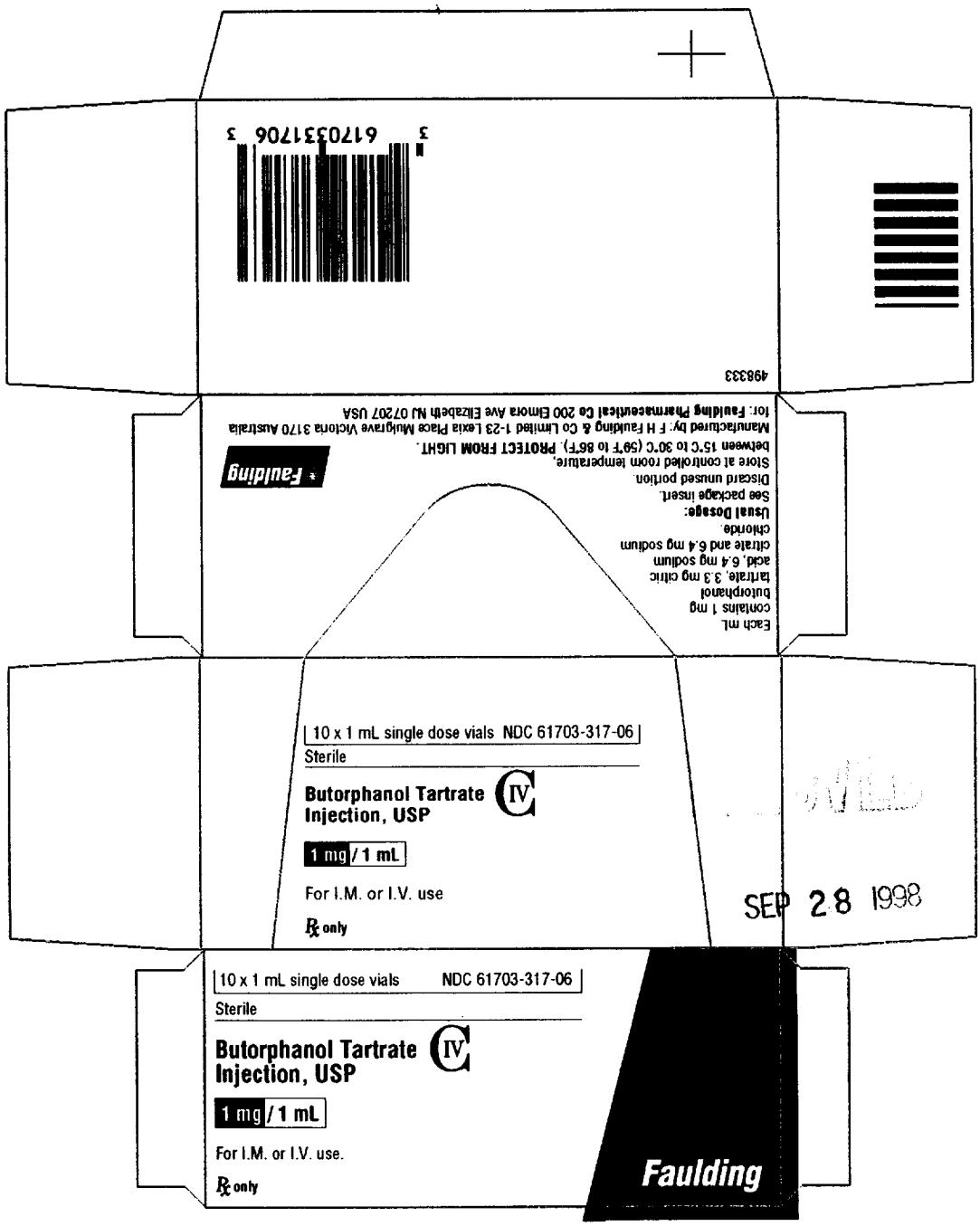
Mary



10 x 2 mL Vials
Size:42.5 x 38.5 x 84.5 mm
Colour: 295 C, 271 C

SAMPLE

Marq



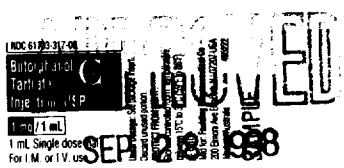
10 x 2 mL Vials
Size:42.5 x 38.5 x 84.5 mm
Colour: 295 C, 199 C

SAMPLE


APPROVED
SEP 28 1998
1 mL Single dose
For I.M. or I.V. use


APPROVED
SEP 28 1998
1 mL Single dose vial
For I.M. or I.V. use


SEP 28 1998
APPROVED


APPROVED
SEP 28 1998
1 mL Single dose
For I.M. or I.V. use

NDC 61703-318-06

Butorphanol Tartrate Injection, USP

2 mg/1 mL

1 mL Single dose vial
For I.M. or I.V. use

SAMPLE

SEP 28 1998

NDC 61703-318-06

Butorphanol Tartrate Injection, USP

2 mg/1 mL

1 mL Single dose vial
For I.M. or I.V. use

SAMPLE

SEP 28 1998

NDC 61703-318-06

Butorphanol Tartrate Injection, USP

2 mg/1 mL

1 mL Single dose vial
For I.M. or I.V. use

SAMPLE

SEP 28 1998

NDC 61703-318-06

Butorphanol Tartrate Injection, USP

2 mg/1 mL

1 mL Single dose vial
For I.M. or I.V. use

SAMPLE

SEP 28 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75170

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 75-170

DRUG PRODUCT: Butorphanol Tartrate Injection USP, 1 mg/mL and 2 mg/mL

FIRM: Faulding Pharmaceutical Co.

DOSAGE FORM: Injection

STRENGTHS: 1 mg/mL and 2 mg/mL

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form :

The drug product will be manufactured, processed, packaged, and tested by:

F.H. Faulding & Co. Limited
1-23 Lexia Place
Mulgrave, Victoria 3170
Australia
(OK on 2-18-98).

Manufacturer-Active Ingredients:

Two manufacturers of the drug substance Butorphanol Tartrate are included in the ANDA:

DMF

DMF

(OK on 2-18-98).

Contract Laboratories:

The following contract firms are listed in the ANDA along with the functions performed by each:

Performs testing on butorphanol tartrate, citric acid, sodium chloride and glass vials.

Performs testing on the nitrogen.

Performed testing on the sodium chloride for the exhibit batch only. Future testing to be done by

(OK on 2-18-98).

BIO STUDY:

A waiver of *in-vivo* bioequivalence study requirements was granted: see review of 10/28/97, Dr. S. Pradhan, HFD-652.

A letter was issued to the applicant 10/29/97 stating that there were no bio questions at that time.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Both the drug substance and drug product are USP 23 item. Methods validation by an FDA laboratory is not required.
Methods verification performed by FDA's Philadelphia District Lab and found satisfactory.

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

Stability protocol: Satisfactory

Expiration date:

24 months expiration date with three month accelerated data (40°C ± 2°C) and room temperature (25°C ± 2°C) data.

The stability data includes the following strength and lots:

Lot # 7011530R 1 mg/mL
Lot # 7011535R 2 mg/mL
Lot # 7021530R 1 mg/mL
Lot # 7021535R 2 mg/mL

LABELING:

Satisfactory per A. Vezza, HFD-613 reviewed on 8/4/98.

STERILIZATION VALIDATION (IF APPLICABLE):

Microbiological review satisfactory - 6/25/98
sterilize the product at 121.6°C for 26 minutes.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Lot # 7011530R 1 mg/mL	vials
Lot # 7011535R 2 mg/mL	vials
Lot # 7021530R 1 mg/mL	vials
Lot # 7021535R 2 mg/mL	vials

DMF was reviewed and found adequate - D. Shostak, HFD-647, 1/28/98.

DMF was reviewed and found adequate by E. Ramos, HFD-645 4/9/98.

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

The stability batch size:

Lot # 7011530R 1 mg/mL	vials
Lot # 7011535R 2 mg/mL	vials
Lot # 7021530R 1 mg/mL	vials
Lot # 7021535R 2 mg/mL	vials

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

The production batch sizes are the same as that of the test batches, i.e., 10L for each strength and have the same manufacturing process as the test batch.

CHEMIST: Lucia C. Tang /S/ DATE: 8-11-98 9-17-98

SUPERVISOR: Ubrani Venkataram. /S/ DATE: 8-13-98 9/17/98

F/T/ by pah/9/16/98
x:\new\firmsam\faulding\ltrs&rev\75170no2.apf
75170AAP.P/Tang/8-10-98

ANDA 75-170

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-170

3. NAME AND ADDRESS OF APPLICANT
Faulding Pharmaceutical Co.
Attention: Sharif Ahmed
200 Elmora Avenue
Elizabeth, NJ 07207

4. LEGAL BASIS FOR SUBMISSION
The listed drug is Stadol® (Butorphanol Tartrate Injection USP, 1 mg/mL and 2 mg/mL) manufactured by Apothecon - NDA 17-857.

The aPplicant certifies that to their knowledge no patents are currently in effect for the drug product and that the drug product is not entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Butorphanol Tartrate Injection USP

8. SUPPLEMENT(s) PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: July 22, 1997

FDA:
Acknowledgement: September 2, 1997
Bio review: October 29, 1997

10. PHARMACOLOGICAL CATEGORY
Opioid analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF

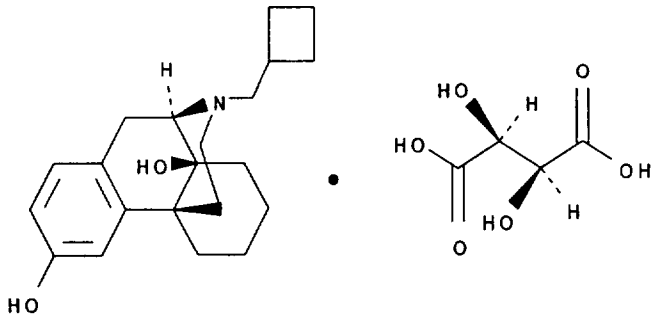
13. DOSAGE FORM
Injection

14. POTENCIES
1 mg/mL & 2 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Butorphanol Tartrate USP

$C_{21}H_{29}NO_2.C_4H_6O_6$; M.W. = 477.56



(-)-17-(Cyclobutylmethyl)morphinan-3,14-diol *D*-(-)-tartrate (1:1) (salt). CAS [58786-99-5]

16. RECORDS AND REPORTS: N/A

17. COMMENTS
   a. Minor CMC deficiencies remain.
   b. Label review is pending as of 2/3/98.
   c. Microbiological review is pending as of 2/3/98.
   d. Method validation not required - USP 23 items.
   e. Bio is satisfactory.
   f. EIR is pending.

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA is NOT APPROVABLE. The amendment will be MINOR.

19. REVIEWER: Donald Shostak

DATE COMPLETED: February 3, 1998

ANDA 75-170

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-170

3. NAME AND ADDRESS OF APPLICANT

Faulding Pharmaceutical Co.
Attention: Sharif Ahmed
200 Elmora Avenue
Elizabeth, NJ 07207

4. LEGAL BASIS FOR SUBMISSION

The listed drug is Stadol® (Butorphanol Tartrate Injection USP, 1 mg/mL and 2 mg/mL) manufactured by Apothecon - NDA 17-857.

The applicant certifies that to their knowledge no patents are currently in effect for the drug product and that the drug product is not entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Butorphanol Tartrate Injection USP

8. SUPPLEMENT(s) PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
Submitted: July 22, 1997
Amendment (Chemistry & label): March 20, 1998 (Subject of this review)
Amendment (Label): 7-24-98

FDA:
Acknowledgement: September 2, 1997
Bio review: October 29, 1997
Label Review: March 5, 1998
Chemistry review # 1 & letter: March 10, 1998
Microbiological review: April 1, 1998
Label OK review: 8-4-98

10. PHARMACOLOGICAL CATEGORY — 11. Rx or OTC

Opioid analgesic — Rx

12. RELATED IND/NDA/DMF(s)

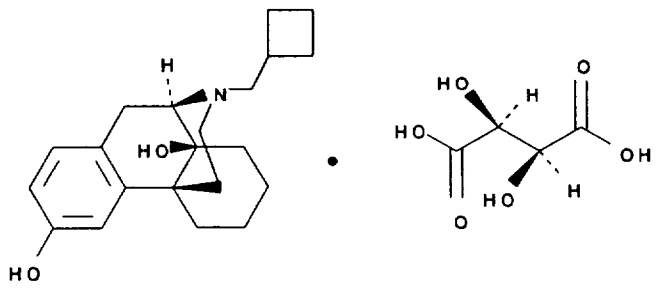
DMF
DMF

13. DOSAGE FORM

14. POTENCIES

Injection

1 mg/mL & 2 mg/mL



15. CHEMICAL NAME AND STRUCTURE:

Butorphanol Tartrate USP

$C_{21}H_{29}NO_2 . C_4H_6O_6$; M.W. =477.56

(-)-17-(Cyclobutylmethyl)morphinan-3,14-diol *D*-(-)-tartrate (1:1) (salt). CAS [58786-99-5]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. CMC issues satisfactory.
b. Label review satisfactory -8/4/98
c. Microbiological review satisfactory - 6/25/98
d. Method verification performed - satisfactory
e. Bio is satisfactory - waiver granted 10/28/97.
f. EIR - overall acceptable 2/18/98.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 8-11-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75170

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-640

Microbiologist's Review #1

March 31, 1998

A. 1. **ANDA** 75-170

APPLICANT Faulding Pharmaceutical Co.
200 Elmora Avenue
Elizabeth New Jersey 07207

2. PRODUCT NAME: Butorphanol Tartrate Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 mg/mL and 2 mg/mL, 1 mL fill in 2 mL Single-Dose Amber Vials, Intravenous and Intramuscular

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Narcotic Analgesic

B. 1. DATE OF INITIAL SUBMISSION: July 22, 1997
Subject of this Review (Received July 23, 1997)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: 3/23/98

C. REMARKS: The subject drug product is filled into 2 mL vials on Filling Line 2 at the pharmaceutical facility in

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments regarding are provided

/S/ 4/1/98
Andrea S. High, Ph. D.

4/3/98

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\75-170
Initialed by F. Fang or F. Holcombe, Jr.

OFFICE OF GENERIC DRUGS, HFD-640
Microbiologist's Review #2
June 25, 1998

A. 1. **ANDA** 75-170

APPLICANT Faulding Pharmaceutical Co.
200 Elmora Avenue
Elizabeth New Jersey 07207

2. PRODUCT NAME: Butorphanol Tartrate Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 mg/mL and 2 mg/mL, 1 mL fill in 2 mL Single-Dose Amber Vials, Intravenous and Intramuscular

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Narcotic Analgesic

B. 1. DATE OF INITIAL SUBMISSION: July 22, 1997
(Received July 23, 1997)

2. DATE OF FAX AMENDMENT: June 19, 1998
Subject of this Review (Received, June 22, 1998)

3. RELATED DOCUMENTS: None
4. ASSIGNED FOR REVIEW: 6/24/98

C. REMARKS: The subject amendment is in response to the Microbiology Deficiencies in the FAX Amendment dated May 20, 1998.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance.

(/S/ 6/25/98
Andrea S. High, Ph. D.

6/25/98

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\75-170a
Initialed by F. Fang or F. Holcombe, Jr.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75170

BIOEQUIVALENCY REVIEW(S)

OCT 28 1997

Butorphanol Tartrate
1 mg/mL and 2 mg/mL Injection, USP
ANDA #75-170
Reviewer: Sikta Pradhan, Ph.D.
WP #75170W.797

Faulding Pharmaceutical Co.
Elizabeth, New Jersey
Submission Date:
July 22, 1997

Review of a Waiver Request

The sponsor has requested a waiver of the in vivo bioequivalence study requirements for its test product, Butorphanol Tartrate Injection USP, 1 mg/mL and 2 mg/mL in 1 mL vials, in accordance with 21 CFR 320.22(b)(1). The reference listed drug (RLD) is Stadol[R] Injection (preservative free, NDA #17-857 of Apothecon).

Butorphanol tartrate is used in the management of pain when the use of an opioid analgesic is appropriate. It is also used in preoperative or preanesthetic medication, as a supplement to balanced anaesthesia and for the relief of pain during labor.

The drug product is an injectable intended solely for intravenous(IV) or intramuscular(IM) administration. (a parenteral solution) 4/14

Table 1
Comparative Formulations

Ingredients	Test Product (mg/mL)	Reference Product (mg/mL)
Butorphanol tartrate, USP	1.0 or 2.0	1.0 or 2.0
Citric Acid, USP	3.3	3.3
Sodium Citrate, USP	6.4	6.4
Sodium Chloride, USP	6.4	6.4
Water for Injection	qs to 1 mL	qs to 1 mL

Comments:

1. Comparative formulations of the test product and RLD presented in Table 1 indicate their identical compositions.

2. The test product and RLD are identical with regard to conditions of use, dosage form, active ingredient, routes of administration, and strengths.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Faulding Pharmaceuticals that its Butorphanol Tartrate Injection, 1mg/mL and 2mg/mL, in 1 mL single-dose vials, falls under 21 CFR 320.22(b)(1) of the Bioavailability /Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of in vivo bioequivalence study be granted. From the bioequivalence point of view, the test product, Butorphanol Tartrate Injection, 1mg/mL and 2mg/mL in 1mL single-dose vials is deemed bioequivalent to the currently approved Stadol[R], 1mg/mL and 2 mg/mL, respectively, manufactured by Apothecon.

The firm should be informed of the recommendation.

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- /S/ 10/24/97

Concur: ---------- /S/ Date: 10/28/97

Rabindra Patnaik, Ph. D.
Acting Director, Division of Bioequivalence

cc: ANDA # 75-170 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File.

SP/10-15-97//X:\wpfile\Pradhan\75170W.797

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75170

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-170** Date of Submission: **July 22, 1997**

Applicant's Name: **Faulding Pharmaceutical Co.**

Established Name: **Butorphanol Tartrate Injection USP, 1 mg/mL, and 2 mg/mL**

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Replace the statement with the symbol "Rx only" or "℞ only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: **http://www.fda.gov/cder/guidance/index.htm** for guidance.

   b. The Federal Register notice dated October 1, 1997 (Volume 62, Number 190) placed butorphanol tartrate into schedule IV of the Controlled Substances Act. As a result the labels and labeling must be revised to comply with 21 CFR 1302.04. We note that the FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "WARNING: May be habit-forming." throughout the labels and labeling of scheduled drugs.

   c. Please revise your temperature storage recommendations throughout your labels and labeling to read:

      Store at controlled room temperature, between 15°C to 30°C (59°F to 86°F).

1. CONTAINER 1 mL vial (1 mg/mL and 2 mg/mL)

   a. See GENERAL COMMENTS above.

b. Replace the
statement with the following statements:

i. **Usual Dosage:** See package insert.

ii. Discard unused portion.

iii. **PROTECT FROM LIGHT.**

c. If space is a concern, the street address is not required and may be deleted.

d. Please improve the print quality and resolution of the print on the side panel. It is difficult to read.

e. What color are the flip-off lids?

2. CARTON 10 x 1 mg/mL and 10 x 2 mg/mL

a. Please see GENERAL COMMENTS and comments (a) and (b) and (c) under CONTAINER.

b. **Usual Dosage:** (capital D).

3. INSERT

a. GENERAL COMMENT

Please revise so that the number and corresponding unit appear on the same line of text (e.g., see CLINICAL PHARMACOLOGY - Pharmacokinetics - "7 ng/mL" and Postoperative Analgesia - "10 mg morphine", and "30 minutes").

b. DESCRIPTION

i. Revise the molecular weight to read "477.56" as per USP 23.

ii. We encourage you to include the pH range for your drug product.

c. CLINICAL PHARMACOLOGY

Clinical Trials

i. ***"Use in the Management of Pain"*** is a subsection and this heading (bold and italics) should be placed immediately above

"*Postoperative Analgesia*".

ii. "*Postoperative Analgesia*", "*Migraine Headache Pain*", "*Preanesthetic Medication*", "*Balanced Anesthesia*", and "*Labor*" are all subsections of "***Use in the Management of Pain***" and should all appear in italics.

d. ADVERSE REACTIONS

Please increase the prominence of the asterisks throughout this section.

e. DRUG USE AND DEPENDENCE

Insert the following text as the first paragraph (see GENERAL COMMENT b above):

Butorphanol tartrate injection is classified by the Drug Enforcement Administration as a Schedule IV controlled substance.

f. DOSAGE AND ADMINISTRATION

Use for Pain - "***Intravenous***" and "***Intramuscular***" are subsection headings and should appear in italics.

g. HOW SUPPLIED

i. See GENERAL COMMENTS (a) and (c) above.

ii. Carton of ten 1 mL...

Please revise your container labels and carton and insert labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75170

CORRESPONDENCE

ANDA 75-170

OCT 29 1997

Faulding Pharmaceutical Co.
Attention: Sharif Ahmed
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Butorphanol Tartrate Injection USP, 1 mg/mL, and 2 mg/mL.

> The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-170

Faulding Pharmaceutical Co. SEP 2 1997
Attention: Sharif Ahmed
200 Elmora Avenue
Elizabeth, NJ 07207

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: Butorphanol Tartrate Injection USP, 1 mg/mL, and 2 mg/mL

DATE OF APPLICATION: July 22, 1997

DATE OF RECEIPT: July 23, 1997

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:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips 8/28/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Faulding Inc
A World of Health

Faulding Pharmaceutical Co.
A subsidiary of Faulding Inc
200 Elmora Avenue
Elizabeth, New Jersey 07207
Telephone (908) 527 9100
Facsimile (908) 527 0649

UPS OVERNIGHT COURIER

July 24, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AMENDMENT
N/AF

RE: ANDA 75-170, Butorphanol Tartrate Injection USP, (1mg/mL and 2mg/mL)

Dear Mr. Sporn:

This response is to your letter dated July 13, 1998, requesting additional labeling revisions. Faulding Hospital Pharmaceutical Co. is hereby submitting for your review the additions included in the revised Package Insert.

Enclosed are twelve (12) copies of the revised Package Insert for your review. Also enclosed is a side-by-side comparison with all differences defined by the use of a different color. If this meets with your approval, please consider this as final printed labeling.

Faulding Pharmaceutical Co. looks forward to your review.

Sincerely,

Iris Feliciano
Regulatory Coordinator
Tel: 908-659-2568
Fax: 908-659-2440

cc: H. Maaser, Ph.D., Director of Regulatory Affairs
Enc.:

RECEIVED
JUL 27 1998
GENERIC DRUGS

Faulding Inc
A World of Health

Faulding Pharmaceutical Co.
A subsidiary of Faulding Inc.
200 Elmora Avenue
Elizabeth, New Jersey 07207
Telephone (908) 527 9100
Facsimile (908) 527 0649

July 22, 1997

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application
Butorphanol Tartrate Injection, USP
1 mg/mL, 1ml; 2 mg/mL, 1ml vials
Original Application

Dear Mr. Sporn,

In accordance with the regulations as promulgated under Section 505(j) of the Federal Food, Drug and Cosmetic Act, as amended, Faulding Pharmaceutical Co. is submitting this Abbreviated New Drug Application for Butorphanol Tartrate Injection, USP, 1 mg/mL, 1 mL and 2 mg/ml, 1 ml vials.

The Archival, Review and Field copies of the Abbreviated New Drug Application have been prepared in accordance with the Guidance for Industry on Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application, published in April 1997. This application is contained in two volumes and contains sterility assurance data.

Faulding is providing the Field Copy of this application to the Office of Generic Drugs in accordance with 21 CFR 314.94. Please note that the required Field Copy certification is contained in Section XXI of the ANDA.

In addition, a debarrement certification in accordance with Section 306(k) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act, is contained in Section XXI of this submission.

A request for waiver of the bioavailability/bioequivalence requirements is contained in Section VI. Butorphanol Tartrate Injection, USP is a ready-to-use solution intended for intravenous or intramuscular administration, contains the same active and inactive ingredients, and contains the same total drug content per container as the listed drug product.

The reference listed drug is Apothecon's Stadol® (Butorphanol Tartrate Injection, USP), which is also a ready-to-use solution product.

If you have any questions concerning this submission, please contact me directly at (908) 659-2433.

Yours sincerely,

Faulding Pharmaceutical Co.

Sharif Ahmed
Regulatory Affairs Associate

Attachments