CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-499

***Name*:** Butorphanol Tartrate Nasal Spray, 10 mg/mL, packaged in a 2.5 mL metered-dose spray pump

***Sponsor*:** Apotex Corp.

***Approval Date*:** December 4, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

APPROVAL LETTER

ANDA 75-499

DEC 4 2002

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for Novex Pharma
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 4, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Butorphanol Tartrate Nasal Spray, 10 mg/mL, packaged in a 2.5 mL metered-dose spray pump.

Reference is also made to your amendments dated August 21 and October 31, 2000; January 15 and November 29, 2001; and April 5, August 12, and August 13, 2002.

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 Nasal Spray, 10 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Stadol® NS™ Nasal Spray, 10 mg/mL, of Bristol Myers Squibb Company Pharmaceutical Research Institute).

Under Section 506A of the Act, 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 FDA 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 FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 12/4/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-499
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-640/T.Wang/11/20/02 T.C. Wang 11/25/02
HFD-647/G.Smith/11/20/02 11/25/02
HFD-617/T.Hinchliffe/11/20/02 11/26/02
HFD-613/C.Park/11/20/02 C Park 11/27/02
HFD-613/L.Golson/11/20/02 A. Vezza for L. Golson 11/26/02

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F/T by TOH/11/20/02

APPROVAL

comments satisfactory
Lilo Lagos
12/3/02

Robert Powell West
12/4/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

LABELING

PRESCRIBING INFORMATION

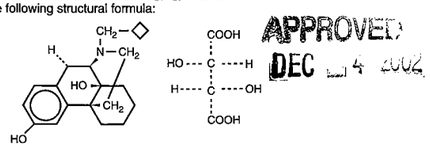
℞ Only C IV

Butorphanol Tartrate Nasal Spray 10 mg/mL

130030

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[S-(R*,R*)]-2,3-dihydroxy-butanedioate (1:1) (salt). The molecular formula is $C_{21}H_{29}NO_2.C_4H_6O_6$, which corresponds to a molecular weight of 477.55 and the following structural formula:



Butorphanol tartrate is a white crystalline substance. 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 Nasal Spray is an aqueous solution of butorphanol tartrate for administration as a metered spray to the nasal mucosa. Each bottle of Butorphanol Tartrate Nasal Spray contains 2.5 mL of a 10 mg/mL solution of butorphanol tartrate with sodium chloride, citric acid, and benzethonium chloride in purified water with sodium hydroxide added to adjust the pH to 4.6 to 5.4. The pump reservoir must be fully primed (see PATIENT INSTRUCTIONS) prior to initial use. After initial priming each metered spray delivers an average of 1 mg of butorphanol tartrate and the 2.5 mL bottle will deliver an average of 14 to 15 doses of Butorphanol Tartrate Nasal Spray. If not used for 48 hours or longer, the unit must be reprimed (see PATIENT INSTRUCTIONS). With intermittent use requiring repriming before each dose, the 2.5 mL bottle will deliver an average of 8 to 10 doses of Butorphanol Tartrate Nasal Spray depending on how much repriming is necessary.

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 the 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 OVERDOSAGE, Treatment section).

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, and within 15 minutes for the nasal spray doses.

Peak analgesic activity occurs within 30 to 60 minutes following intravenous and intramuscular administration and within 1 to 2 hours following the nasal spray administration.

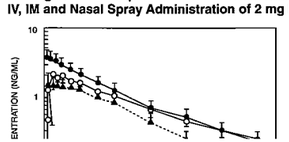
The duration of analgesia varies depending on the pain model as well as the route of administration, but is generally 3 to 4 hours with IM and IV doses as defined by the time 50% of patients required remedication. In postoperative studies, the duration of analgesia with IV or IM butorphanol was similar to morphine, meperidine, and pentazocine when administered in the same fashion at equipotent doses (see Clinical Trials). Compared to the injectable form and other drugs in this class, butorphanol tartrate nasal spray has a longer duration of action (4 to 5 hours) (see Clinical Trials).

Pharmacokinetics

After nasal administration, mean peak blood levels of 0.9 to 1.04 ng/mL occur at 30 to 60 minutes after a 1 mg dose (see Table 1). The absolute bioavailability of butorphanol tartrate nasal spray is 60 to 70% and is unchanged in patients with allergic rhinitis. In patients using a nasal vasoconstrictor (oxymetazoline) the fraction of the dose absorbed was unchanged, but the rate of absorption was slowed. The peak plasma concentrations were approximately half those achieved in the absence of the vasoconstrictor.

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

Figure 1 - Butorphanol Plasma Levels After IV, IM and Nasal Spray Administration of 2 mg Dose



was approximately tripled and total body clearance was approximately one half (half-life 16.8 hours, clearance 92 L/h) compared to healthy subjects (half-life 4.8 hours, clearance 175 L/h). The exposure of hepatically impaired patients to butorphanol was significantly greater (about 2-fold) than that in healthy subjects. Similar results were seen after nasal administration. No effect on C_{max} or T_{max} was observed after a single intranasal dose.

For further recommendations refer to PRECAUTIONS, Hepatic and Renal Disease, Drug Interactions, and Geriatric Use sections and to the CLINICAL PHARMACOLOGY, Individualization of Dosage section 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).

Studies with butorphanol tartrate nasal spray have been performed in postoperative (general, orthopedic, oral, cesarean section) pain, in postepisiotomy pain, in pain of musculoskeletal origin, and in migraine headache pain (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 injection, onset and peak analgesic effect occurred by the time of 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.

The analgesic efficacy of butorphanol tartrate nasal spray was evaluated (approximately 35 patients per treatment group) in a general and orthopedic surgery trial. Single doses of butorphanol tartrate nasal spray (1 or 2 mg) and IM meperidine (37.5 or 75 mg) were compared. Analgesia provided by 1 and 2 mg doses of butorphanol tartrate nasal spray was similar to 37.5 and 75 mg meperidine, respectively, with onset of analgesia within 15 minutes and peak analgesic effect within 1 hour. The median duration of pain relief was 2.5 hours with 1 mg butorphanol tartrate nasal spray, 3.5 hours with 2 mg butorphanol tartrate nasal spray and 3.3 hours with either dose of meperidine.

In a postcesarean section trial, butorphanol tartrate nasal spray administered to 35 patients as two 1 mg doses 60 minutes apart was compared with a single 2 mg dose of butorphanol tartrate nasal spray or a single 2 mg IV dose of butorphanol tartrate injection (37 patients each). Onset of analgesia was within 15 minutes for all butorphanol tartrate regimens. Peak analgesic effects of 2 mg intravenous butorphanol tartrate injection and butorphanol tartrate nasal spray were similar in magnitude. The duration of pain relief provided by both 2 mg butorphanol tartrate nasal spray regimens was approximately 4.5 hours and was greater than intravenous butorphanol tartrate injection (2.6 hours).

Migraine Headache Pain: The analgesic efficacy of two 1 mg doses one hour apart of butorphanol tartrate nasal spray in migraine headache pain was compared with a single dose of 10 mg IM methadone (31 and 32 patients, respectively). Significant onset of analgesia occurred within 15 minutes for both butorphanol tartrate nasal spray and IM methadone. Peak analgesic effect occurred at 2 hours for butorphanol tartrate nasal spray and 1.5 hours for methadone. The median duration of pain relief was 6 hours with butorphanol tartrate nasal spray and 4 hours with methadone as judged by the time when approximately half of the patients remedicated.

In two other trials in patients with migraine headache pain, a 2 mg initial dose of butorphanol tartrate nasal spray followed by an additional 1 mg dose 1 hour later (76 patients) was compared with either 75 mg IM meperidine (24 patients) or placebo (72 patients). Onset, peak activity and duration were similar with both active treatments; however, the incidence of adverse experiences (nausea, vomiting, dizziness) was higher in these two trials with the 2 mg initial dose of butorphanol tartrate nasal spray than in the trial with the 1 mg initial dose.

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 the appropriate sections in PRECAUTIONS).

The usual recommended dose for initial nasal administration is 1 mg (1 spray in **one** nostril). If adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given.

The initial dose sequence outlined above may be repeated in 3 to 4 hours as required after the second dose of the sequence.

For the management of severe pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients additional doses should not be given for 3 to 4 hours. The incidence of adverse events is higher with an initial 2 mg dose (see Clinical Trials).

The initial dose sequence in elderly patients and patients with renal or hepatic impairment should be limited to 1 mg followed, if needed, by 1 mg in 90 to 120 minutes. The repeat dose sequence in these patients should be determined by the patient's response rather than at fixed times but will generally be no less than at 6 hour intervals (see PRECAUTIONS).

INDICATIONS AND USAGE

Butorphanol tartrate nasal spray is indicated for the management of pain when the use of an opioid analgesic is appropriate.

CONTRAINDICATIONS

Butorphanol tartrate nasal spray is contraindicated in patients hypersensitive to butorphanol tartrate or the preservative benzethonium chloride in Butorphanol Tartrate Nasal Spray.

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 and Dependence

Drug Abuse: Butorphanol tartrate, by all routes of administration, has been associated with episodes of abuse. Of the cases received, there were more reports of abuse with the nasal spray formulation than with the injectable formulation.

Physical Dependence, Tolerance and Withdrawal: Prolonged, continuous use of butorphanol tartrate may result in physical dependence or tolerance (a decrease in response to a given dose). Abrupt cessation of use by patients with physical dependence may result in symptoms of withdrawal.

Note - Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical dependence (see DRUG

KEEP OUT OF THE REACH OF CHILDREN.

PATIENT INSTRUCTIONS

Butorphanol Tartrate Nasal Spray 10 mg/mL C

Take medication as directed by your physician. For proper use of the nasal spray, read the following instructions carefully.

NOTE: VIALS DO NOT APPEAR "FULL". THEY ARE PRE-FILLED TO DELIVER ON AVERAGE 14-15 ONE (1) MG DOSES. (THE USUAL DOSE IS 1 MG - ONE SPRAY IN ONE NOSTRIL.)

THE UNIT MUST BE PRIMED WITH ONE OR TWO STROKES IF NOT USED FOR 48 HOURS OR LONGER.

Note: With intermittent use requiring repriming before each dose, the 2.5 mL bottle will deliver an average of 8-10 doses of Butorphanol Tartrate Nasal Spray.

USUAL DOSE: ONE Spray. Spray ONLY ONCE into ONLY ONE nostril. DO NOT spray into both nostrils unless directed by your doctor. DO NOT repeat sooner than directed by your doctor.

Fig. 1

1. Blow nose gently to clear both nostrils. (Fig. 1)

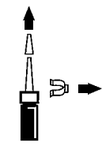


Fig. 2

2. Pull clear cover off pump unit. Remove protective clip from neck of pump unit. (Fig. 2)

Fig. 3

3. Prime Butorphanol Tartrate Nasal Spray 10 mg/mL by placing nozzle between first and second finger with thumb on the bottom of bottle. Pump sprayer unit FIRMLY and QUICKLY until a fine spray appears (up to 7-8 strokes). (Fig. 3)

Fig. 4

4. Insert spray tip approximately 1 cm (width of small finger) into one nostril, pointing the tip toward the back of the nose. (Fig. 4)

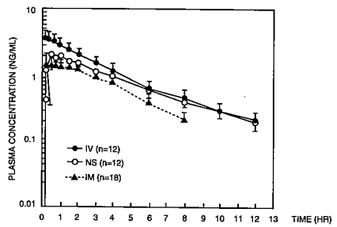
5. Close other nostril with your forefinger and tilt head slightly forward. (Fig. 5)

FOLD HERE AND DISPENSE TO PATIENT - DETACH HERE AND DISPENSE TO PATIENT

and is unchanged in patients with allergic rhinitis. In patients using a nasal vasoconstrictor (oxymetazoline) the fraction of the dose absorbed was unchanged, but the rate of absorption was slowed. The peak plasma concentrations were approximately half those achieved in the absence of the vasoconstrictor.

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

Figure 1 - Butorphanol Plasma Levels After IV, IM and Nasal Spray 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).

Table 1
Mean Pharmacokinetic Parameters of Butorphanol in Young and Elderly Subjects[a]

	Intravenous		Nasal	
Parameters	**Young**	**Elderly**	**Young**	**Elderly**
T_{max}[b](hr)			0.62(0.32)[e] (0.15-1.50)[g]	1.03(0.74) (0.25-3.00)
C_{max}[c] (ng/mL)			1.04(0.40) (0.35-1.97)	0.90(0.57) (0.10-2.68)
AUC (inf)[d] (hr-ng/mL)	7.24(1.57) (4.40-9.77)	8.71(2.02) (4.76-13.03)	4.93(1.24) (2.16-7.27)	5.24(2.27) (0.30-10.34)
Half-life (hr)	4.56(1.67) (2.06-8.70)	5.61(1.36) (3.25-8.79)	4.74(1.57) (2.89-8.79)	6.56(1.51) (3.75-9.17)
Absolute Bio-availability (%)			69(16) (44-113)	61(25) (3-121)
Volume of Distribution[f] (L)	487(155) (305-901)	552(124) (305-737)		
Total Body Clearance (L/hr)	99(23) (70-154)	82(21) (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) Time to peak plasma concentration.
c) Peak plasma concentration normalized to 1 mg dose.
d) Area under the plasma concentration-time curve after a 1 mg dose.
e) Mean (1 S.D.)
f) Derived from IV data.
g) (range of observed values)

Dose proportionality for butorphanol tartrate nasal spray has been determined at steady state in doses up to 4 mg at 6 hour intervals. Steady state is achieved within 2 days. The mean peak plasma concentration at steady state was 1.8-fold (maximal 3-fold) following a single dose.

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

Butorphanol is extensively metabolized in the liver. Metabolism is qualitatively and quantitatively similar following intravenous, intramuscular, or nasal 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 (≃ 5-fold) occurs when butorphanol is dosed to steady state (1 mg transnasally q6h for 5 days).

Elimination occurs by urine and fecal excretion. When ^3H labelled 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.

Butorphanol pharmacokinetics in the elderly differ from younger patients (see Table 1). The mean absolute bioavailability of butorphanol tartrate nasal spray in elderly women (48%) was less than that in elderly men (75%), young men (68%) or young women (70%). Elimination half-life is increased in the elderly (6.6 hours as opposed to 4.7 hours in younger subjects).

In renally impaired patients with creatinine clearances <30 mL/min, the elimination half-life was approximately doubled and the total body clearance was approximately one half (10.5 hours [clearance 150 L/h] compared to 5.8 hours [clearance 260 L/h] in healthy subjects). No effect on C_{max} or T_{max} was observed after a single dose.

After intravenous administration to patients with hepatic impairment, the elimination half-life of butorphanol

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 and Dependence
Drug Abuse: Butorphanol tartrate, by all routes of administration, has been associated with episodes of abuse. Of the cases received, there were more reports of abuse with the nasal spray formulation than with the injectable formulation.

Physical Dependence, Tolerance and Withdrawal: Prolonged, continuous use of butorphanol tartrate may result in physical dependence or tolerance (a decrease in response to a given dose). Abrupt cessation of use by patients with physical dependence may result in symptoms of withdrawal.

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

PRECAUTIONS
General
Hypotension associated with syncope during the first hour of dosing with butorphanol tartrate nasal spray has been reported rarely, particularly in patients with past history of similar reactions to opioid analgesics. Therefore, patients should be advised to avoid activities with potential risks.

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
The initial dose sequence of butorphanol tartrate nasal spray should be limited to 1 mg followed, if needed, by 1 mg in 90-120 minutes. The repeat dose sequence in these patients should be determined by the patient's response rather than at fixed times but will generally be at intervals of no less than 6 hours (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Individualization of Dosage sections).

Cardiovascular Effects
Because butorphanol may increase the work of the heart, especially the pulmonary circuit, 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 (see CLINICAL PHARMACOLOGY).

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) Butorphanol is one of a class of drugs known to be abused and thus should be handled accordingly (see DRUG ABUSE AND DEPENDENCE section).
4) Patients should be instructed on the proper use of butorphanol nasal spray (see PATIENT INSTRUCTIONS).

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.

In healthy volunteers, the pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol tartrate nasal spray were not affected by the co-administration of a single 6 mg subcutaneous dose of sumatriptan. However, in another study in healthy volunteers, the pharmacokinetics of butorphanol were significantly altered (29% decrease in AUC and 38% decrease in C_{max}) when a 1 mg dose of butorphanol tartrate nasal spray was administered 1 minute after a 20 mg dose of sumatriptan nasal spray. (The two drugs were administered in opposite nostrils.) When the butorphanol tartrate nasal spray was administered 30 minutes after the sumatriptan nasal spray, the AUC of butorphanol increased 11% and C_{max} decreased 18%. In neither case were the pharmacokinetics of sumatriptan affected by co-administration with butorphanol tartrate nasal spray. These results suggest that the analgesic effect of butorphanol tartrate nasal spray may be diminished when it is administered shortly after sumatriptan nasal spray, but by 30 minutes any such reduction in effect should be minimal.

The safety of using butorphanol tartrate nasal spray and Imitrex® (sumatriptan) nasal spray during the same episode of migraine has not been established. However, it should be noted that both products are capable of producing transient increases in blood pressure.

The pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol tartrate nasal spray were not affected by the co-administration of cimetidine (300 mg QID). Conversely, the administration of butorphanol tartrate nasal spray (1 mg butorphanol QID) did not alter the pharmacokinetics of a 300 mg dose of cimetidine.

It is not known if the effects of butorphanol are altered by other concomitant medications that affect hepatic

PHARMACIST - DETACH HER

Fig. 5

5. Close other nostril with your forefinger and tilt head slightly forward. (Fig. 5)

Fig. 6

6. Pump spray unit firmly and quickly by pushing down on the "finger grips" of the pump unit and against the thumb at the bottom of the bottle. Sniff gently with your mouth closed. (Fig. 6)

Fig. 7

7. After spraying, remove pump unit from nose. Tilt your head backwards and sniff gently a few more seconds. (Fig. 7)

8. Your doctor will tell you whether a two spray dose is needed. If needed, administer a second spray in the other nostril, following steps 4-7. Replace protective clip and clear cover, respectively, (Fig. 2) after each dose.

When not in use, store spray unit in child-resistant container.

Butorphanol Tartrate Nasal Spray should not be used by anyone other than the person for whom it was prescribed. To prevent this, and to reduce the chance of children taking the drug it is important to dispose of any excess Butorphanol Tartrate Nasal Spray just as soon as it is no longer needed.

The best way to safely dispose of the unit is to unscrew the cap, rinse the bottle and spray assembly under the water faucet, and dispose of the parts in a waste can where children cannot easily get to them.

Manufactured by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Manufactured for:
Apotex Corp.
Weston, FL 33326

130030 February 2002

MEDICATION GUIDE

Butorphanol Tartrate Nasal Spray 10 mg/mL C IV

Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

What is the most important information I should know about butorphanol tartrate nasal spray?

- **Your doctor has prescribed butorphanol tartrate nasal spray to treat your pain. The medication in butorphanol tartrate nasal spray belongs to a group of medicines that is known to cause dependence and abuse. Butorphanol tartrate nasal spray causes these effects only in a small number of patients. However, because it can have these effects, it is VERY IMPORTANT that you not use butorphanol tartrate nasal spray more often or in larger doses than your doctor has instructed. Also, it is important to have regular checkups with your doctor to ensure that you're using butorphanol tartrate nasal spray correctly. The longer you use butorphanol tartrate nasal spray, the greater your risk of getting dependent on it.**
- **Because butorphanol tartrate nasal spray may make you feel sleepy or dizzy, do not drive or operate dangerous machinery, e.g., automobiles until you can no longer feel the effects of the drug. Also, do not drink alcohol while using butorphanol tartrate nasal spray because it may worsen any side effects.**

What is butorphanol tartrate nasal spray?
Butorphanol tartrate nasal spray is an opioid narcotic pain reliever that is used for the relief of pain when the use of an opioid pain medication is appropriate. Butorphanol tartrate nasal spray comes in the form of a nasal spray. One spray of butorphanol tartrate nasal spray is quickly absorbed in the nasal passages.

What do I need to know about using a strong opioid narcotic pain reliever such as butorphanol tartrate nasal spray?
Butorphanol tartrate nasal spray has been reported to be abused. Do not use butorphanol tartrate nasal spray more often or in larger doses than instructed by your doctor. Follow your doctor's instructions **exactly** and have regular checkups with your doctor when using butorphanol tartrate nasal spray to ensure you are using butorphanol tartrate nasal spray properly.

Who should not take butorphanol tartrate nasal spray?
Butorphanol tartrate nasal spray should not be used if you have ever had an allergic reaction to the active ingredient, butorphanol, or if you are allergic to benzethonium chloride, a preservative in Butorphanol Tartrate Nasal Spray. Butorphanol tartrate nasal spray should not be used by patients less than 18 years old. Butorphanol tartrate has been found in the breast milk of women who are using butorphanol tartrate nasal spray. Therefore, butorphanol tartrate nasal spray should not be used by patients who are breastfeeding. Patients over the age of 65 years may need less butorphanol tartrate nasal spray than younger patients.

You should not use butorphanol tartrate nasal spray if you are dependent on another narcotic medicine. Dependence is when you **need** the medicine and you can't perform normally unless you are taking it.

How should I take butorphanol tartrate nasal spray?
Use butorphanol tartrate nasal spray only as directed by your doctor. Never use butorphanol tartrate nasal spray more often or in larger doses than instructed by your doctor. Since you may experience sleepiness or dizziness, use butorphanol tartrate nasal spray in a comfortable location where you can lie down if necessary.

Usual Dosing
If your doctor prescribed a 1 mg dose of butorphanol tartrate nasal spray for relief of pain:

- Spray ***one*** spray into ***one*** nostril - one spray is a 1 mg dose. This is the most common initial dose. If prescribed by your doctor, a second spray may be taken **60 to 90 minutes** after the first if needed for pain relief. If instructed by your doctor, the above sequence may be repeated every 3 to 4 hours as needed for pain relief. If your pain hasn't lessened or it becomes worse, please contact your doctor immediately.

If your doctor prescribed a 2 mg dose of butorphanol tartrate nasal spray for relief of pain:

- Spray ***one*** spray in ***each*** nostril - two sprays equal a 2 mg dose. If instructed by your doctor, this dose of butorphanol tartrate nasal spray may be repeated every 3 to 4 hours as needed for pain relief. If your pain hasn't lessened or it becomes worse, please contact your doctor immediately.

If you have liver or kidney disease, you may need to take butorphanol tartrate nasal spray less often or in a lower dose. Elderly patients may also need to take a lower dose of butorphanol tartrate nasal spray.

Use and Storage of Nasal Spray Unit
Your pharmacist will assemble the nasal spray unit. However, you **must prime** the unit before using it the first time and if it has not been used for 48 hours or longer. NOTE: VIALS DO NOT APPEAR "FULL". THEY ARE PREFILLED TO DELIVER ON AVERAGE 14 TO 15 ONE (1) mg DOSES. If you only use butorphanol tartrate nasal spray occasionally and need to reprime it each time, the vial will deliver an average of 8 to 10 doses of Butorphanol Tartrate Nasal Spray. See additional instructions below for priming and using the spray

PHARMACIST - DETACH HERE

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.

The fraction of butorphanol tartrate nasal spray absorbed is unaffected by the concomitant administration of a nasal vasoconstrictor (oxymetazoline), but the rate of absorption is decreased. Therefore, a slower onset can be anticipated if butorphanol tartrate nasal spray is administered concomitantly with, or immediately following, a nasal vasoconstrictor.

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

Information for Patients (see PRECAUTIONS, Use in Ambulatory Patients)
See accompanying Medication Guide and Patient Instructions.

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/m² for mice and 354 mg/m² 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/m²) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/m²) 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/m²) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (360 mg/m²) and 60 mg/kg/oral (720 mg/m²) also showed higher incidences of post-implantation loss in rabbits.

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

Labor and Delivery
Butorphanol tartrate nasal spray is not recommended during labor or delivery because there is no clinical experience with its use in this setting.

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 mcg/L of milk in a mother receiving 2 mg IM four times a day).

Although there is no clinical experience with the use of butorphanol tartrate nasal spray in nursing mothers, it should be assumed that butorphanol will appear in the milk in similar amounts following the nasal route of administration.

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
Of the approximately 1500 patients treated with butorphanol tartrate injection in clinical studies, 15% were 61 years of age or older and 1% were 76 years or older. Of the approximately 1700 patients treated with butorphanol tartrate nasal spray in clinical studies, 8% were 65 years of age or older and 2% were 75 years or older.

Due to changes in clearance, the mean half-life of butorphanol is increased by 25% (to over 6 hours) in patients over the age of 65 years (see CLINICAL PHARMACOLOGY, Pharmacokinetics section). Elderly patients may be more sensitive to the side effects of butorphanol. In clinical studies of butorphanol tartrate nasal spray, elderly patients had an increased frequency of headache, dizziness, drowsiness, vertigo, constipation, nausea and/or vomiting, and nasal congestion compared with younger patients. There are insufficient efficacy data for patients ≥65 years to determine whether they respond differently from younger patients.

Initially a 1 mg dose of butorphanol tartrate nasal spray should generally be used in geriatric patients and 90-120 minutes should elapse before administering a second 1 mg dose, if needed (see CLINICAL PHARMACOLOGY, Individualization of Dosage section).

Butorphanol and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS
Clinical Trial Experience
A total of 2446 patients were studied in premarketing clinical trials of butorphanol. 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-term and long-term clinical trials in patients receiving butorphanol by any route. There has been no attempt to correct for placebo effect or to 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 butorphanol tartrate nasal spray were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with butorphanol tartrate 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 in clinical trials, 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, stomach pain
Nervous: anxiety, confusion, dizziness, euphoria, floating feeling, insomnia, nervousness, paresthesia, somnolence, tremor
Respiratory: bronchitis, cough, dyspnea, epistaxis, nasal congestion, nasal irritation, pharyngitis, rhinitis, sinus congestion, sinusitis, upper respiratory infection

The initial dose sequence outlined above may be repeated in 3 to 4 hours as required after the second dose of the sequence.

Depending on the severity of the pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients single additional 2 mg doses should not be given for 3 to 4 hours.

Use in Balanced Anesthesia
The use of butorphanol tartrate nasal spray is not recommended because it has not been studied in induction or maintenance of anesthesia.

Labor
The use of butorphanol tartrate nasal spray is not recommended as it has not been studied in labor.

Safety and Handling
Butorphanol tartrate nasal spray is an open delivery system with increased risk of exposure to health care workers.

In the priming process, a certain amount of butorphanol may be aerosolized; therefore, the pump sprayer should be aimed away from the patient or other people or animals.

The disposal of Schedule IV controlled substances must be consistent with State and Federal Regulations. The unit should be disposed of by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

HOW SUPPLIED
Butorphanol Tartrate Nasal Spray is supplied in a child-resistant prescription vial containing a metered-dose spray pump with protective clip and dust cover, a bottle of nasal spray solution, and an insert containing Prescribing Information, Patient Instructions and a Medication Guide. On average, one bottle will deliver 14 to 15 doses if no repriming is necessary.
NDC 60505-0813-1 - 10 mg per mL, 2.5 mL bottle.

Storage Conditions
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].

PHARMACIST ASSEMBLY INSTRUCTIONS
FOR BUTORPHANOL TARTRATE NASAL SPRAY
The pharmacist will assemble Butorphanol Tartrate Nasal Spray prior to dispensing to the patient, according to the following instructions:

1) Open the child-resistant prescription vial and remove the spray pump and solution bottle.
2) Assemble Butorphanol Tartrate Nasal Spray by first unscrewing the white cap from the solution bottle and screwing the pump unit tightly onto the bottle. Make sure the clear cover is on the pump unit.
3) Return the Butorphanol Tartrate Nasal Spray bottle to the child-resistant prescription vial for dispensing to the patient.

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Who should not take butorphanol tartrate nasal spray?
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You should not use butorphanol tartrate nasal spray if you are dependent on another narcotic medicine. Dependence is when you **need** the medicine and you can't perform normally unless you are taking it.

How should I take butorphanol tartrate nasal spray?
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unit.

What should I avoid while taking butorphanol tartrate nasal spray?

- Because butorphanol tartrate nasal spray may make you feel sleepy or dizzy, do not drive or operate dangerous machinery, e.g., automobiles until you no longer feel the effects of the drug.
- Do not drink alcohol while using butorphanol tartrate nasal spray because it may worsen drowsiness, dizziness and your general ability to function appropriately.
- Some medications cannot be taken with butorphanol tartrate nasal spray because of unwanted side effects. Before you begin using butorphanol tartrate nasal spray, as well as while you are using it, be sure to tell your doctor about any and all other drugs you are taking, including those sold without a prescription (over-the-counter). Do not take any other medicine, including any over-the-counter medicine, unless directed to do so by a doctor who knows you are using butorphanol tartrate nasal spray.
- Because butorphanol tartrate nasal spray may cause harm to an unborn child, tell your doctor if you are pregnant or planning to become pregnant.
- Because small amounts of butorphanol tartrate may appear in breast milk, be sure to consult with your doctor if you are nursing an infant.
- Because of butorphanol tartrate nasal spray's potential to cause dependence or abuse, be sure to tell your doctor if you ever had a problem with overuse of drugs or alcohol.

What are the possible side effects of butorphanol tartrate nasal spray?

The type and frequency of side effects experienced by patients taking butorphanol tartrate nasal spray are those commonly seen with opioid narcotic pain relievers. The most frequently reported side effects in studies with butorphanol tartrate were drowsiness, dizziness, nausea and/or vomiting. In studies where patients used butorphanol tartrate nasal spray for up to 6 months, nasal congestion and difficulty sleeping were frequently reported.

Butorphanol tartrate nasal spray may affect your breathing. This side effect is serious but unlikely if butorphanol tartrate nasal spray is taken as instructed. Notify your doctor immediately if you experience shortness of breath or other difficulty breathing.

Butorphanol tartrate nasal spray may affect your blood pressure or your heart rate. Notify your doctor immediately if you feel lightheaded, have an irregular heart beat or have headaches that you did not have before you started taking butorphanol tartrate nasal spray.

Side effects other than those listed above have occurred in some patients. For example, the following side effects have been reported rarely, but may be disturbing if they do occur: visual blurring, dysphoria (feeling of sadness, unpleasantness, or discomfort), floating feeling, and hallucinations. Notify your doctor or pharmacist if any side effects persist or become troublesome.

What do I do if someone takes an overdosage of butorphanol tartrate nasal spray?

If you suspect that someone may have taken an overdosage of this medicine, contact your local poison control center or emergency room immediately.

This medication was prescribed for your current condition. Do not use butorphanol tartrate nasal spray for another condition or give the drug to others. Keep butorphanol tartrate nasal spray and all medicines out of the reach of children. Discard any unused portion of the medicine by removing the cap, rinsing the bottle and spray assembly under the water faucet, and disposing the parts in a waste can where children cannot easily get to them.

This summary does not include everything there is to know about butorphanol tartrate nasal spray. Medicines are sometimes prescribed for uses other than those listed. If you have questions or concerns, or want more information about butorphanol tartrate nasal spray, your doctor and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace a careful discussion with your doctor.

130030 February 2002

E AND DISPENSE TO PATIENT

Skin and Appendages: sweating/clammy, pruritus
Special Senses: blurred vision, ear pain, tinnitus, unpleasant taste

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

Cardiovascular: hypotension, syncope
Nervous: abnormal dreams, agitation, dysphoria, hallucinations, hostility, withdrawal symptoms
Skin and Appendages: rash/hives
Urogenital: impaired urination

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 under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.

Body as a Whole: edema
Cardiovascular: chest pain, hypertension, tachycardia
Nervous: depression
Respiratory: shallow breathing

Postmarketing Experience

Postmarketing experience with butorphanol tartrate nasal spray has shown an adverse event profile similar to that seen during the premarketing evaluation of butorphanol by all routes of administration. Adverse experiences that were associated with the use of butorphanol tartrate nasal spray or butorphanol tartrate injection and that are not listed above have been chosen for inclusion below because of their seriousness, frequency of reporting, or probable relationship to butorphanol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These adverse experiences include apnea, convulsion, delusion, drug dependence, excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements, overdose, and vertigo. Reports of butorphanol overdose with a fatal outcome have usually but not always been associated with ingestion of multiple drugs.

DRUG ABUSE AND DEPENDENCE

Butorphanol tartrate nasal spray is listed in Schedule IV of the Controlled Substances Act (CSA).

Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical 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 continuous basis for an extended period.

Clinical Trial Experience

In all clinical trials, less than 1% of patients using butorphanol tartrate nasal spray had experiences that suggested the development of physical dependence or tolerance. Much of this information is based on experience with patients who did not have prolonged continuous exposure to butorphanol tartrate nasal spray. However, in one controlled clinical trial where patients with chronic pain from nonmalignant disease were treated with butorphanol tartrate nasal spray (n=303) or placebo (n=99) for up to 6 months, overuse (which may suggest the development of tolerance) was reported in nine (2.9%) patients receiving butorphanol tartrate nasal spray and no patients receiving placebo. Probable withdrawal symptoms were reported in eight (2.6%) patients using butorphanol tartrate nasal spray and no patients receiving placebo in the chronic nonmalignant pain study. Most of these patients abruptly discontinued butorphanol tartrate nasal spray after extended use or high doses. Symptoms suggestive of withdrawal included anxiety, agitation, tremulousness, diarrhea, chills, sweats, insomnia, confusion, incoordination, 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.

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 individual response to the effects of opiates. The most serious symptoms are hypoventilation, cardiovascular insufficiency, coma, and death. Butorphanol overdose may be associated with ingestion of multiple drugs (see ADVERSE REACTIONS, Postmarketing Experience section).

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 determining 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 sections). 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

The usual recommended dose for initial nasal administration is 1 mg (1 spray in **one** nostril). Adherence to this dose reduces the incidence of drowsiness and dizziness. If adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given.

Usual Dosing

If your doctor prescribed a 1 mg dose of butorphanol tartrate nasal spray for relief of pain:

- Spray ***one*** spray into ***one*** nostril - one spray is a 1 mg dose. This is the most common initial dose. If prescribed by your doctor, a second spray may be taken **60 to 90 minutes** after the first if needed for pain relief. If instructed by your doctor, the above sequence may be repeated every 3 to 4 hours as needed for pain relief. If your pain hasn't lessened or it becomes worse, please contact your doctor immediately.

If your doctor prescribed a 2 mg dose of butorphanol tartrate nasal spray for relief of pain:

- Spray ***one*** spray in ***each*** nostril - two sprays equal a 2 mg dose. If instructed by your doctor, this dose of butorphanol tartrate nasal spray may be repeated every 3 to 4 hours as needed for pain relief. If your pain hasn't lessened or it becomes worse, please contact your doctor immediately.

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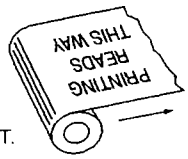
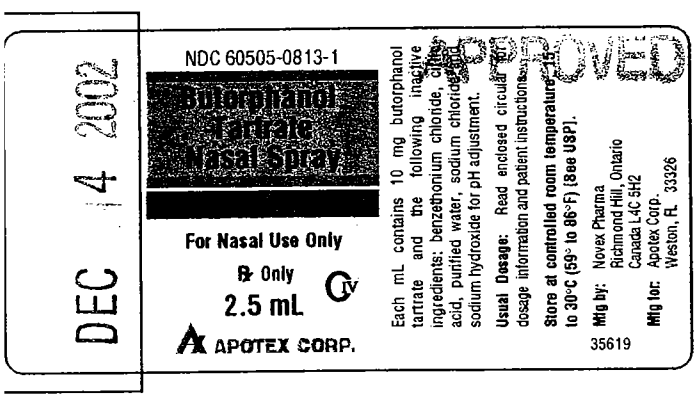
Manufactured by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Manufactured for:
Apotex Corp.
Weston, FL
33326

130030 February 2002

) Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2
Phone: (905) 884-2050
Fax: (905) 884-9876

RIALS / LABEL STANDARD SPECIFICATIONS			Date December 20, 2001
'phanol Tartrate Nasal Spray 10 mg/mL			Label Size 2.375" x 1.1875"
Litho anent	Web Direction Label on OUTSIDE of roll. Copy printed WITH the roll. Left side of label OFF FIRST. 	Colour (s) Black Blue - 300C PMS 3125C Red PMS 1788C UV Varnish	Change Revise text as per FDA labelling deficiency letter dated Dec. 2001
	Date: 12/20/01	Reg. Affairs Revision No.: 1	☐ ☐



Enlarged to 150%
By FOIA STAFF

NTED PACKAGING MATERIALS / LABEL STANDARD SPECIFICATIONS				Date December 20, 2001
0033	Product Name: Butorphanol Tartrate Nasal Spray 10 mg/mL			Label Size 144.463 mm x 84.138 mm
xopress	Paper Stock: Satin Litho	Web Direction: Label on OUTSIDE of roll. Copy printed WITH the roll. left side of label OFF FIRST. (PRINTING READS THIS WAY)	Colour (s): Black, Pantone Blue 300 C, Pantone Red 1788 C, Pantone 3125 C, UV Varnish	Change: Revise text as per FDA Labelling deficiency letter dated Dec. 2001
#	Adhesive: Permanent			
	Date: 12/20/01	Reg. Affairs Revision No.: 2	☐ AS IS ☐ NEW PROOF REQ.	

Spray ONCE into ONE nostril only. DO NOT spray into both nostrils unless directed by your physician. Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].

NDC 60505-0813-1

Butorphanol Tartrate Nasal Spray

[redacted]

For Nasal Use Only

℞ Only C IV

2.5 mL

Bottle and Spray Pump

APOTEX CORP.

PHARMACY LABEL TO START HERE
ATTENTION PHARMACIST:
Please remove tamper evident seal. Assemble unit prior to dispensing. Assembly instructions included in Prescribing Information (inside). Remove Prescribing Information before dispensing.
Dispense with Patient Instructions and Medication Guide.

APPROVED DEC 4 2002

Manufactured by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Manufactured for:
Apotex Corp.
Weston, FL 33326
130033

UPC Code

128C Bar Code

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

LABELING REVIEWS

This review supersedes the review dated April 6, 1999

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

ANDA Number: **75-499** Dates of Submission: **November 3, 1998 and January 28, 1999**

Applicant's Name: **Novex Pharma**

Established Name: **Butorphanol Tartrate Nasal Spray, 1 mg/spray 10 mg/mL 2.5 mL**

Labeling Deficiencies:

1. CONTAINER 2.5 mL

   a. We note that your storage recommendations on the container label are "Store between 59°-86°F (15°-30°C)" while in your insert there is "Store [redacted]". Please revise to read "Store below 25°C (77°F)".

   b. Please include the controlled substance symbol on the main panel. We refer you to 21 CFR 1302.04 for guidance.

2. PATIENT INSTRUCTIONS

   Satisfactory, in draft.

3. MEDICATION GUIDE

   Please note that as of June 16, 1998 the reference listed drug provides for a patient medication guide for this drug product. You must also submit this labeling piece to your application. We have included a copy of the approval letter for this piece as well as a copy of the medication guide. The text of this medication guide must also appear at the end of the insert labeling and must be referred to in the PRECAUTIONS, Information for Patients subsection. See 21 CFR 201.57(f)(2) for guidance.

4. INSERT

   a. GENERAL COMMENTS

      i. This review was based on the labeling for STADOL NS (BMS, approved April 16, 1999).

ii. Please be consistent with the formatting of your subsection titles. Some are of the same prominence as the section titles.

iii. Use "to" rather than a hyphen when expressing a range of values.

b. TITLE

Include the controlled substance symbol with the title.

c. DESCRIPTION

i. Chemical name - ... (cyclo... [delete hyphen]

ii. Revise the molecular weight to be "477.56".

iii. "1 mg" rather than "1.0 mg".

d. CLINICAL PHARMACOLOGY

i. General Pharmacology and Mechanism of Action, first sentence - 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.

ii. Pharmacodynamics, second sentence - ... within 15 minutes for intramuscular ...

iii. Table 1 - Improve the legibility of the superscripts in this table.

iv. Pharmacokinetics

A). Sixth paragraph - ... and Nursing Mothers under PRECAUTIONS).

B). Paragraph beginning "The major ..."

1). Second sentence - ... 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 (≅ 5-fold) occurs when butorphanol is dosed to steady state (1 mg transnasally q6h for 5 days).

2). Delete the last sentence.

C). Paragraph beginning "About 5% ..." - Delete.

D). Last sentence - ... refer to **PRECAUTIONS: Hepatic and Renal Disease, Drug Interactions,** and **Geriatric Use** sections and to **the CLINICAL PHARMACOLOGY, Individualization of Dosage** section below.

v. Clinical Trials, second sentence - ... tartrate injection (This revision should be made in general.)

vi. Postoperative

A). Retitle this "Postoperative Pain".

B). First paragraph, last sentence - "40 mg"

C). Third paragraph, penultimate sentence - "analgesic" rather than "analgesia" (second occurrence)

D). Last sentence - "(2.6 hours)"

vii. Delete the "Preanesthetic Medication", "Balanced Anesthesia" and "Labor" subsections.

viii. Individualization of Dosage

A). Delete the first and third paragraphs.

B). Paragraph beginning "The initial dose ..."

"... in 3 to 4 hours as required after the second dose of the sequence."

e. WARNINGS

Add the following subsections after the second paragraph:

Drug Abuse and Dependence

Drug Abuse

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

Physical Dependence, Tolerance and Withdrawal

Prolonged, continuous use of butorphanol tartrate may result in physical dependence or tolerance (a decrease in response to a given dose). Abrupt cessation of use by patients with physical dependence may result in symptoms of withdrawal.

Note - Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical dependence (see DRUG ABUSE AND

DEPENDENCE section below).

f. PRECAUTIONS

i. Hepatic and Renal Disease

Last sentence - ... (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

ii. Cardiovascular Effects - Relocate "(see CLINICAL PHARMACOLOGY) to the end of the first paragraph.

iii. Use in Ambulatory Patients

A). Relocate this subsection to be after the "Cardiovascular Effects" subsection.

B). Revise this subsection as follows:

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 ... 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. Butorphanol is one of a class of drugs known to be abused and thus should be handled accordingly (see **DRUG ABUSE AND DEPENDENCE** section).
4. Patients should be instructed on the proper use of butorphanol nasal spray (See PATIENT INSTRUCTIONS).

iv. Drug Interactions

A). Add the following as the second paragraph:

In healthy volunteers, the pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol tartrate nasal spray were not affected by the coadministration of a single

6 mg subcutaneous dose of sumatriptan.

B). Add the following as the third paragraph:

The pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol nasal spray were not affected by the co-administration of cimetidine (300 mg QID). Conversely, the administration of butorphanol nasal spray (1 mg butorphanol QID) did not alter the pharmacokinetics of a 300 mg dose of cimetidine.

C). Fourth paragraph (formerly second), first sentence - ... altered by other concomitant ... of drugs (erythromycin ...

v. Information for Patients

A). Relocate this subsection to immediately follow the "Drug Interactions" subsection.

B). Revise the text of this subsection heading to read: Information for Patients (See PRECAUTIONS, Use in Ambulatory Patients.) and delete the remaining text.

C). Please reference the MEDICATION GUIDE and the Patient Instructions in this subsection. See 21 CFR 201.57(f)(2).

vi. Carcinogenesis, Mutagenesis, Impairment of Fertility

A). Revise the first paragraph to read as follows:

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.

B). "m^2" rather than "sq.m."

vii. Pregnancy -

A). See (f)(vi)(B) above.

B). First paragraph, third sentence -

... 30 mg/kg/oral (360 mg/m^2) and 60 mg/kg/oral (720 mg/m^2) also ...

C). Second paragraph - Delete [redacted] (two instances).

viii. Labor and Delivery, first paragraph

A). First sentence

1). There have ... (delete [redacted]).

2). ... during labor. The reports ...

B). Last sentence - ... pregnancies. (See OVERDOSAGE, Treatment)

ix. Nursing Mothers, second sentence - "mcg/L" rather than "microgram/liter"

x. Geriatric Use

A). First paragraph, last sentence - ... (see CLINICAL PHARMACOLOGY, Individualization ...

B). Second paragraph, first sentence - ... 65 years. Elderly ...

g. ADVERSE REACTIONS

i. First paragraph, second sentence - ... remainder receiving butorphanol ...

ii. Second paragraph - ... by any route. There ...

iii. Third paragraph, second sentence - Delete [redacted]

iv. Fourth paragraph

A). ... or greater in clinical trials, and were ...

B). Delete the asterisks, the capitalization, and the parenthetical percentages in this subsection

C). Special Senses - Delete " [redacted].

D). Delete [redacted]

v. The following adverse experiences were reported with a frequency of less than 1% in clinical trials, and were ..."

vi. Nervous - ... agitation, dysphoria, hallucinations, hostility, withdrawal symptoms

vii. Delete [redacted]
(two instances)

viii. Paragraph beginning "The following infrequent ...

First sentence - ... and under circumstances ...

ix. Cardiovascular - chest pain, hypertension, tachycardia

x. Nervous - Delete [redacted].

xi. Respiratory - Delete [redacted].

xii. Add the following as the last subsection in this section:

Postmarketing Experience
Postmarketing experience with butorphanol tartrate nasal spray has shown an adverse event profile similar to that seen during the premarketing evaluation of butorphanol by all routes of administration. Adverse experiences that were associated with the use of butorphanol tartrate nasal spray or butorphanol tartrate injection and that are not listed above have been chosen for inclusion below because of their seriousness, frequency of reporting, or probable relationship to butorphanol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These adverse experiences include apnea, convulsion, delusion, drug dependence, excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements, overdose, and vertigo. Reports of butorphanol overdose with a fatal outcome have usually but not always been associated with ingestion of multiple drugs.

h. DRUG ABUSE AND DEPENDENCE

Revise this section as follows:

Butorphanol tartrate nasal spray is listed in Schedule IV of the Controlled Substances Act (CSA).

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 continuous basis for an extended period.

Clinical Trial Experience
In all clinical trials, less than 1% of patients using butorphanol tartrate nasal spray had experiences that

suggested the development of physical dependence or tolerance. Much of this information is based on experience with patients who did not have prolonged continuous exposure to butorphanol tartrate nasal spray. However, in one controlled clinical trial where patients with chronic pain from nonmalignant disease were treated with butorphanol tartrate nasal spray (n=303) or placebo (n=99) for up to 6 months, overuse (which may suggest the development of tolerance) was reported in nine (2.9%) patients receiving butorphanol tartrate nasal spray and no patients receiving placebo. Probable withdrawal symptoms were reported in eight (2.6%) patients using butorphanol tartrate nasal spray and no patients receiving placebo in the chronic nonmalignant pain study. Most of these patients abruptly discontinued butorphanol tartrate nasal spray after extended use or high doses. Symptoms suggestive of withdrawal included anxiety, agitation, tremulousness, diarrhea, chills, sweats, insomnia, confusion, incoordination, 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.

i. OVERDOSAGE

i. First paragraph - ... of butorphanol overdose ... of opioid drugs in general. Consequences of overdose vary with the amount of butorphanol ingested and individual response to the effects of opiates. The most serious symptoms are ... insufficiency, coma, and death. Butorphanol overdose may be associated with ingestion of multiple drugs (see **ADVERSE REACTIONS: Postmarketing Experience** section).

ii. "Treatment" is a subsection of the "OVERDOSAGE" section and the heading should have the same prominence as "Clinical Manifestations".

iii. Add the following as the last paragraph:

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

j. DOSAGE AND ADMINISTRATION

i. Decrease the prominence of the subsection headings.

ii. First paragraph, second sentence - ... CLINICAL PHARMACOLOGY, Individualization of Dosage).

iii. Use for Pain, second paragraph - The initial dose ... 3 to 4 hours as required after the second dose of the sequence.

iv. Use in Balanced Anesthesia - ... butorphanol tartrate nasal spray is ...

v. Labor - Delete the first paragraph.

vi. Safety and Handling - Add the following as the first sentence of the last paragraph:

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

k. HOW SUPPLIED

i. Storage Conditions - Store below 25°C (77°F).

ii. Please include the full text of the MEDICATION GUIDE and the Patient Instructions at the end of the insert.

Please revise your container labels and insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachments: Innovator approval letter and MEDICATION GUIDE

Copy of Reference Listed Drug labeling removed.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels:

Patient Instructions:

Medication Guide:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Stadol NS®

NDA Number: 19-890

NDA Drug Name: Stadol NS® (butorphanol tartrate) Nasal Spray

NDA Firm: Bristol-Myers Squibb

Date of Approval of NDA Insert and supplement #: 4/16/99 (S-014)
Medication guide 6/16/98 (S-013)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	

Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? YES If so, is NDA and/or ANDA in a light resistant container? AMBER GLASS BOTTLE	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date			

for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. The container label has "Store between 15°-30°C.", the insert has "Store ————, and the innovator has "Store below 25°C." I have asked the firm to revise to be the same as the innovator. Do you concur?

2. The firm has the pH adjusted to ———— while the innovator has a pH of 5. Is this acceptable?

3. The USP monograph for Butorphanol Tartrate Injection states that the product should be protected from light. Is this product also light sensitive? Does the applicant's container protect the product from light?

FOR THE RECORD:

1. The model for the insert is the labeling for STADOL NS (BMS, approved 4/16/99 NDA 19-890/S-014). S-013, approved 6-16-98, was for the Medication Guide.

2. The inactives are accurately listed in the DESCRIPTION section (p 94 v 1.1).

3. Novex Pharma is the manufacturer (p 182 v 1.1).

4. The container is a 5 mL amber glass bottle (p 352 v 1.1).

5. This insert is a combined insert with the parenteral form of the drug. The ADVERSE REACTIONS section was left intact since it was not possible to separate the adverse reactions for the two dosage forms.

6. The DESCRIPTION section says the product's pH is adjusted to between ———— while the innovator's product is at pH 5. I have asked the chemist about this.

7. The container label has "Store at CRT.", the insert has "Store————.", while the innovator insert has "Store below 25°C." and container has "Store below 30°C." I asked the chemist about this. I told the firm to use "Store ———— because I believe this to be the most recent statement.

8. The firm has filed under Paragraph IV. The patent expires 8/7/01.

9. I left both the graph (Figure 1) and Table I intact (leaving in the parenteral information).

10. I left in the following portions of text concerning the parenteral form of the drug because I felt it is useful information: CLINICAL PHARMACOLOGY - Pharmacodynamics 3rd paragraph, Use in Management of Pain 2nd paragraph; and PRECAUTIONS - The Labor & Delivery and Nursing Mothers subsections. After discussion with Charlie Hoppes we shall be asking the firm to remove the Preanesthetic Medication, Balanced Anesthesia, and Labor subsections from the CLINICAL PHARMACOLOGY section because the nasal spray does not have these indications. The studies have to do with the parenteral form of the drug.

Date of Review: 4-2-99 Dates of Submission: 11-3-98 & 1-28-99

Primary Reviewer: Adolph Vezza Date:

A. Vezza 5/25/99

Team Leader: Charlie Hoppes Date:

5/25/99

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cc:

ANDA: 75-499
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: **75-499** Date of Submission: **June 29, 2000**

Applicant's Name: **Novex Pharma**

Established Name: **Butorphanol Tartrate Nasal Spray, 1 mg/spray**
10 mg/mL (2.5 mL)

Labeling Deficiencies:

1. CARTON

   We note that you have not submitted carton labeling for your drug product. Please submit and/or comment.

2. PATIENT INSTRUCTIONS

   a. We note you have submitted computer-generated printer's proof as your final printed Patient Instructions Leaflet. Although we will accept printer's proof for container labels and carton labeling, you must submit final printed Patient Instructions Leaflet prior to the approval of this application.

   b. First "NOTE" – "1" rather than "l"

3. MEDICATION GUIDE

   a. See comment above under (a) PATIENT INSTRUCTIONS

   b. Although we believe that the printing size of Medication Guide (printed along with Patient Instructions) meets the minimum requirement, it is rather difficult to read your labeling due to the poor quality of printing. We strongly encourage you to increase the readability of your Medication Guide.

   c. Boxed Statements – First item, second sentence:

      ...nasal spray belongs to a group of... [delete ' ——————— ']

   d. Who should not take butorphanol tartrate nasal spray? – Third sentence:

      Butorphanol tartrate has been found... [delete ———————]

   e. What should I avoid while taking butorphanol tartrate nasal spray? – Penultimate bullet:

      Delete ——————— ".

4. INSERT

   a. You may delete the terms "PRESCRIBING INFORMATION" if you adopt to do so.

   b. DESCRIPTION

      i. Molecular formula – Add a comma between "O_2" and "C_4".

      ii. Revise the molecular weight to read "477.55".

c. CLINICAL PHARMACOLOGY

i. General Pharmacology and Mechanism of Action – First paragraph:

... an antagonist at k-opioid receptors. ["k" should appear with proper prominence]

ii. Clinical Trials (Use in the Management of Pain, Migraine Headache Pain) – Last sentence:

... with the 1 mg... [add "the"]

d. PRECAUTIONS (Labor and Delivery)

Upon further review we ask that you delete the first two paragraphs, which are specifically associated with injection form of butorphanol tartrate.

e. HOW SUPPLIED

We encourage the relocation of the storage requirement statement so that it appears in this section, not in the Medication Guide.

Please revise your labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels:

Patient Instructions:

Medication Guide:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Stadol NS®

NDA Number: 19-890

NDA Drug Name: Stadol NS® (butorphanol tartrate) Nasal Spray

NDA Firm: Bristol-Myers Squibb

Date of Approval of NDA Insert and supplement #: 4/16/99 (S-014)
Medication guide 6/16/98 (S-013)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels:

Other Comments:

NOTES/QUESTIONS TO THE CHEMIST (Addressed in the last review)

1. **The container label has "Store between 15°-30°C.", the insert has "Store ————", and the innovator has "Store below 25°C." I have asked the firm to revise to be the same as the innovator. Do you concur?**

2. **The firm has the pH adjusted to ———— while the innovator has a pH of 5. Is this acceptable?**

3. **The USP monograph for Butorphanol Tartrate Injection states that the product should be protected from light. Is this product also light sensitive? Does the applicant's container protect the product from light?**

FOR THE RECORD:

1. **The model for the insert is the labeling for STADOL NS (BMS, approved 4/16/99 NDA 19-890/S-014). S-013, approved 6-16-98, was for the Medication Guide.**

2. **The inactives are accurately listed in the DESCRIPTION section (p 94 v 1.1).**

3. Novex Pharma is the manufacturer (p 182 v 1.1).

4. The container is a 5 mL amber glass bottle (p 352 v 1.1).

5. This insert is a combined insert with the parenteral form of the drug. The ADVERSE REACTIONS section was left intact since it was not possible to separate the adverse reactions for the two dosage forms.

6. The DESCRIPTION section says the product's pH is adjusted to between ——— while the innovator's product is at pH 5. I have asked the chemist about this.

7. The container label has "Store at CRT.", the insert has "Store ———.", while the innovator insert has "Store below 25°C." and container has "Store below 30°C." I asked the chemist about this. I told the firm to use "Store below 25°C." because I believe this to be the most recent statement.

8. The firm has filed under Paragraph IV. The patent expires 8/7/01.

9. I left both the graph (Figure 1) and Table I intact (leaving in the parenteral information).

10. I left in the following portions of text concerning the parenteral form of the drug because I felt it is useful information: CLINICAL PHARMACOLOGY – Pharmacodynamics 3rd paragraph, Use in Management of Pain 2nd paragraph; and PRECAUTIONS – The Labor & Delivery and Nursing Mothers subsections.

The following is a portion of FTR from 75-759 (ESI LEDERLE) review.

5. This insert of RLD is a combined insert with the parenteral form of the drug. The ADVERSE REACTIONS section was left intact since it was not possible to separate the adverse reactions for the two dosage forms.

6. All information regarding comparison between injection and nasal form of this product under CLINICAL PHARMACOLOGY was retained without carving out the injection information (e.g., Figure 1 & Table 1). This is based on a previous decision made during the review for ANDA 75-499 (Novex).

7. Information specific to the injection form only under PRECAUTIONS section has been carved out.

8. The nasal form is not indicated for use during "Labor". Therefore, any information specifically associated with "labor" has been carved out except the "Labor" subsection under PRECAUTIONS and D &A sections, which states that "The use of butorphanol tartrate nasal spray is not recommended as it has not been studied in labor".

Date of Review: July 6, 2000 Date of Submission: June 29, 2000

Primary Reviewer: Chan Park C Park Date: 7/7/00

Team Leader: Charlie Hoppes A. Vezza for Date: 7/7/00

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

ANDA Number: **75-499** Date of Submission: **May 25, 2001**

Applicant's Name: **Novex Pharma**

Established Name: **Butorphanol Tartrate Nasal Spray, 1 mg/spray**
10 mg/mL (2.5 mL)

Labeling Deficiencies:

1. GENERAL

   Upon further review, we ask that you revise the storage temperature requirement to read "Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F) [see USP]".

2. CONTAINER

   a. See general comment above.

   b. Revise the text "[redacted]" to read "Usual Dosage: Read enclosed circular for dosage information and patient instructions.".

   c. Please assure that your packaging system meets the requirement found in 21 CFR 1302.06. Please include information on your provision in your next chemistry amendment.

3. CARTON

   a. See general comment above.

   b. Please include the net quantity statement. We suggest the following:

      2.5 mL Bottle and Spray Pump

   c. Boxed statement "Pharmacy label... dispensing.".

      i. Please assure that you allow enough space for the pharmacy label.

      ii. Add the following text as the last sentence in a prominent manner:

         Dispense with patient instructions and medication guide.

4. PATIENT INSTRUCTIONS

   Please assure that your patient instruction can be easily detached (*i.e.*, perforated) from the professional package insert.

5. MEDICATION GUIDE

   See comment above under PATIENT INSTRUCTIONS.

6. INSERT

   a. See general comment above.

b. The insert labeling for the reference listed drug has been recently revised and approved on January 5, 2001. Please revise your insert labeling to be in accordance with the attached Stadol NS® insert labeling. We remind you that you must not include information regarding the use of your drug product during "labor" as that indication is restricted to the injection.

Please revise your labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: A copy of the Stadol NS® package insert labeling

Copy of Reference Listed Drug labeling removed.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels:

Patient Instructions:

Medication Guide:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Stadol NS®

NDA Number: 19-890

NDA Drug Name: Stadol NS® (butorphanol tartrate) Nasal Spray

NDA Firm: Bristol-Myers Squibb

Date of Approval of NDA Insert and supplement #: 1/5/2001 (S-015)
Medication guide 6/16/98 (S-013)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels:

Other Comments:

NOTES/QUESTIONS TO THE CHEMIST (Addressed in the last review)

1. **The firm has the pH adjusted to ——— while the innovator has a pH of 5. Is this acceptable?**

2. **The USP monograph for Butorphanol Tartrate Injection states that the product should be protected from light. Is this product also light sensitive? Does the applicant's container protect the product from light?**

3. **Please see the comment 2(c) above. (sent to the chemist via e-mail on 6/18/01)**

FOR THE RECORD:

1. **The model for the insert is the labeling for STADOL NS (BMS, approved 1/5/01 NDA 19-890/S-015). S-014, approved 6-16-98, was for the Medication Guide.**

2. **The inactives are accurately listed in the DESCRIPTION section (p 94 v 1.1).**

3. **Novex Pharma is the manufacturer (p 182 v 1.1).**

4. The container is a 5 mL amber glass bottle (p 352 v 1.1).

5. This insert is a combined insert with the parenteral form of the drug. The ADVERSE REACTIONS section was left intact since it was not possible to separate the adverse reactions for the two dosage forms.

6. The DESCRIPTION section says the product's pH is adjusted to between ——— while the innovator's product is at pH 5. I have asked the chemist about this.

7. Storage temperature

   RLD – Store at 25°C (77°F) controlled room temperature. See USP

   ANDA – Store ———

   We asked the firm to revise to read "Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F) [see USP]".

8. The firm has filed under Paragraph IV. The patent expires 8/7/01.

9. I left both the graph (Figure 1) and Table I intact (leaving in the parenteral information).

10. I left in the following portions of text concerning the parenteral form of the drug because I felt it is useful information: CLINICAL PHARMACOLOGY – Pharmacodynamics 3rd paragraph, Use in Management of Pain 2nd paragraph; and PRECAUTIONS – The Labor & Delivery and Nursing Mothers subsections.

The following is a portion of FTR from 75-759 (ESI LEDERLE) review.

11. This insert of RLD is a combined insert with the parenteral form of the drug. The ADVERSE REACTIONS section was left intact since it was not possible to separate the adverse reactions for the two dosage forms.

12. All information regarding comparison between injection and nasal form of this product under CLINICAL PHARMACOLOGY was retained without carving out the injection information (e.g., Figure 1 & Table 1). This is based on a previous decision made during the review for ANDA 75-499 (Novex).

13. Information specific to the injection form only under PRECAUTIONS section has been carved out.

14. The nasal form is not indicated for use during "Labor". Therefore, any information specifically associated with "labor" has been carved out except the "Labor" subsection under PRECAUTIONS and D &A sections, which states that "The use of butorphanol tartrate nasal spray is not recommended as it has not been studied in labor".

Date of Review: June 11, 2001 Date of Submission: May 25, 2001

Primary Reviewer: Chan Park Date:

Team Leader: Charlie Hoppes Date:

---

cc:

ANDA: 75-499
DUP/DIVISION FILE
HFD-613/CPark/CHeppes (no cc)
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Review

6/18/01

6/18/01

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: **75- 499** Date of Submission: **November 16, & January 18, 2002**

Applicant's Name: **Novex Pharma**

Established Name: **Butorphanol Tartrate Nasal Spray, 1 mg/spray**
10 mg/mL (2.5 mL)

Labeling Deficiencies:

1. CONTAINER

   a. We note that you have submitted only one copy of FPL in this submission. You are required to submit 12 copies. We refer you to 21 CFR 314.94(a)(8)(ii) for guidance.

   b. Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please assure that these criteria are met prior to submission of final print.

2. CARTON

   See comments under CONTAINER.

3. INSERT

   a. GENERAL

      i. As addressed in the Tele-conference between Marcy Macdonald of your firm and Chan Park of the Agency on January 28 and January 30, 2002, the following comment is based on the last approved labeling for Stadol® Nasal Spray (approved on January 14, 2002).

      ii. See comment (a) under CONTAINER.

   b. PRECAUTIONS (Drug Interactions)

      i. Revise the second paragraph to read as follows:

      ... a single 6 mg subcutaneous dose of sumatriptan. However, in another study in healthy volunteers, the pharmacokinetics of butorphanol were significantly altered (29% decrease in AUC and 38% decrease in C_{max}) when a 1 mg dose of butorphanol tartrate nasal spray was administered 1 minute after a 20 mg dose of sumatriptan nasal spray. (The two drugs were administered in opposite nostrils.) When the butorphanol tartrate nasal spray was administered 30 minutes after the sumatriptan nasal spray, the AUC of butorphanol increased 11% and C_{max} decreased 18%. In neither case was the pharmacokinetics of sumatriptan affected by co-administration with butorphanol tartrate nasal spray. These results suggest that the analgesic effect of butorphanol tartrate nasal spray may be diminished when it is administered shortly after sumatriptan nasal spray, but by 30 minutes any such reduction in effect should be minimal.

ii. Include the following text as the new third paragraph:

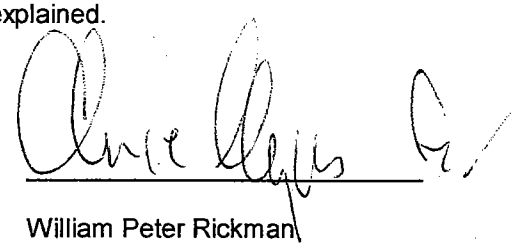
The safety of using butorphanol tartrate nasal spray and Imitrex® (sumatriptan) nasal spray during the same episode of migraine has not been established. However, it should be noted that both products are capable of producing transient increases in blood pressure.

[Please include a disclaimer stating that Imitrex® is the registered trademark of Glaxo Wellcome, Inc.]

Please revise your labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.



William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels:

Patient Instructions:

Medication Guide:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Stadol NS®

NDA Number: 19-890

NDA Drug Name: Stadol NS® (butorphanol tartrate) Nasal Spray

NDA Firm: Bristol-Myers Squibb

Date of Approval of NDA Insert and supplement #: 1/14/02 (S-017)
Medication guide 6/16/98 (S-013)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels:

Other Comments:

FOR THE RECORD:

1. **The model for the insert is the labeling for STADOL NS (BMS, approved 1/14/02 NDA 19-890/S-017). S-014, approved 6-16-98, was for the Medication Guide.**

2. **The inactives are accurately listed in the DESCRIPTION section (p 94 v 1.1).**

3. **Novex Pharma is the manufacturer (p 182 v 1.1).**

4. **The container is a 5 mL AMBER GLASS bottle (p 352 v 1.1).**

5. **This insert is a combined insert with the parenteral form of the drug. The ADVERSE REACTIONS section was left intact since it was not possible to separate the adverse reactions for the two dosage forms.**

6. **The DESCRIPTION section says the product's pH is adjusted to between ———— while the innovator's product is at pH 5. I have asked the chemist about this.**

7. **Storage temperature**

   RLD – Store at 25°C (77°F) controlled room temperature. See USP

ANDA – Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F) [see USP]".

8. The firm has filed under Paragraph IV. The patent expires 8/7/01.

9. I left both the graph (Figure 1) and Table I intact (leaving in the parenteral information).

10. I left in the following portions of text concerning the parenteral form of the drug because I felt it is useful information: CLINICAL PHARMACOLOGY – Pharmacodynamics 3rd paragraph, Use in Management of Pain 2nd paragraph.

11. The sponsor has submitted an amendment on November 16, 2001 prior to receipt of our deficiency letter based on the Agency's May 25, 2001. This deficiency letter was forwarded to the sponsor on 12/11/01 and the firm submitted another amendment on 1/18/02 in response to the letter. This review is prepared on the submission of 1/18/02.

12. The sponsor proposed a tamper-evident induction seal on the opening of the bottle to meet 21 CFR 1302.06 requirement. See page 2 in this submission.

[The following is a portion of FTR from 75-759 (ESI LEDERLE) review.]

13. This insert of RLD is a combined insert with the parenteral form of the drug. The ADVERSE REACTIONS section was left intact since it was not possible to separate the adverse reactions for the two dosage forms.

14. All information regarding comparison between injection and nasal form of this product under CLINICAL PHARMACOLOGY was retained without carving out the injection information (e.g., Figure 1 & Table 1). This is based on a previous decision made during the review for ANDA 75-499 (Novex).

15. Information specific to the injection form only under PRECAUTIONS section has been carved out.

16. The nasal form is not indicated for use during "Labor". Therefore, any information specifically associated with "labor" has been carved out except the "Labor" subsection under PRECAUTIONS and D &A sections, which states that "The use of butorphanol tartrate nasal spray is not recommended as it has not been studied in labor".

17. We notified all ANDA holders for this product of the labeling changes on Jan. 28, 2002.

Date of Review: 1/30/02 Date of Submission: 1/28/02

Primary Reviewer: Chan Park Date: 2/7/02

Team Leader: Charlie Hoppes Date: 2/7/02

cc:

ANDA: 75-499
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Review

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-499** Date of Submission: **March 6, 2002**

Applicant's Name: **Novex Pharma**

Established Name: **Butorphanol Tartrate Nasal Spray, 1 mg/spray**
10 mg/mL (2.5 mL)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels - 2.5 mL

Satisfactory in FPL as of 3/5/02 submission

Carton Labeling - 1 x 2.5 mL

Satisfactory in FPL as of 3/5/02 submission

Patient Instructions/Medication Guide (printed on each side) - Rev. 2/2002, Code 130030

Satisfactory in FPL as of 3/5/02 submission

Professional Package Insert Labeling - Rev. 2/2002, Code 130030

Satisfactory in FPL as of 3/5/02 submission

Post-Approval Revision Needed - Primary Container:

Increase the prominence of the controlled substance symbol on the primary container labels per 21 CFR 1302.04

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Stadol NS®

NDA Number: 19-890

NDA Drug Name: Stadol NS® (butorphanol tartrate) Nasal Spray

NDA Firm: Bristol-Myers Squibb

Date of Approval of NDA Insert and supplement #: 1/14/02 (S-017)
Medication guide 6/16/98 (S-013)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels:

FOR THE RECORD:

1. The model for the insert is the labeling for STADOL NS (BMS, approved 1/14/02 NDA 19-890/S-017). S-014, approved 6-16-98, was for the Medication Guide.

2. The inactives are accurately listed in the DESCRIPTION section (p 94 v 1.1).

3. Novex Pharma is the manufacturer (p 182 v 1.1).

4. The container is a 5 mL AMBER GLASS bottle (p 352 v 1.1).

5. This insert is a combined insert with the parenteral form of the drug. The ADVERSE REACTIONS section was left intact since it was not possible to separate the adverse reactions for the two dosage forms.

6. The DESCRIPTION section says the product's pH is adjusted to between 4.6 and 5.4 while the innovator's product is at pH 5. It is acceptable.

7. Storage temperature

   RLD – Store at 25°C (77°F) controlled room temperature. See USP

   ANDA – Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F) [see USP]".

8. The firm has filed under Paragraph IV. The patent expired on 8/7/01.

9. I left both the graph (Figure 1) and Table I intact (leaving in the parenteral information).

10. I left in the following portions of text concerning the parenteral form of the drug because I felt it is useful information: CLINICAL PHARMACOLOGY – Pharmacodynamics 3rd paragraph, Use in Management of Pain 2nd paragraph.

11. The sponsor proposed a tamper-evident induction seal on the opening of the bottle to meet 21 CFR 1302.06 requirement. See page 2 in this submission.

[The following is a portion of FTR from 75-759 (ESI LEDERLE) review.]

12. This insert of RLD is a combined insert with the parenteral form of the drug. The ADVERSE REACTIONS section was left intact since it was not possible to separate the adverse reactions for the two dosage forms.

14. All information regarding comparison between injection and nasal form of this product under CLINICAL PHARMACOLOGY was retained without carving out the injection information (e.g., Figure 1 & Table 1). This is based on a previous decision made during the review for ANDA 75-499 (Novex).

15. Information specific to the injection form only under PRECAUTIONS section has been carved out.

16. The nasal form is not indicated for use during "Labor". Therefore, any information specifically associated with "labor" has been carved out except the "Labor" subsection under PRECAUTIONS and D &A sections, which states that "The use of butorphanol tartrate nasal spray is not recommended as it has not been studied in labor".

17. We notified all ANDA holders for this product of the labeling changes on Jan. 28, 2002.

18. The new insert labeling approved in S-017 (approved on 2/7/02) addresses the drug interaction between this product and Imitrex (sumatriptan) under PRECAUTIONS section. We asked to the new drug division on 2/25/02 whether this would affect the medication

guide resulting in the guide reflecting this interaction, but never have the response back.

Date of Review: 3/29/02 **Date of Submission: 3/5/02**

Primary Reviewer: Chan Park Date: 4/1/02

Acting **Team Leader: ~~Charlie Hoppes~~** Lillie Golson Date: 4/1/02

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cc:

ANDA: 75-499
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Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

CHEMISTRY REVIEWS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 1

2. **ANDA #** 75-499

3. **NAME AND ADDRESS OF APPLICANT**
Novex Pharma
380 Eligin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

U.S. Agent:
Apotex Corp.
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061
Attention: Marcfy MacDonald
Associated Director, Regulatory Affair

4. **LEGAL BASIS FOR SUBMISSION**
The reference listed drug is Stadol® NS™ (10 mg/mL Butorphanol Tartrate), Manufactured by Bristol Myers Squibb (NDA 19-890).
U.S. Patent Number 4464378, University of Kentucky Research foundation, expiring August 7, 2001.
There is no unexpired exclusivity for this product.

The firm filed a paragraph IV patent certification, in accordance with 21 CFR 314.94 (a) (12)(I)(A)(4) and Section 505 (j)(2)(A)(vii)(IV) of the Act.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
Stadol® NS™ Nasal Spray

7. **NONPROPRIETARY NAME**
Butorphanol Tartrate
Nasal Spray

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

9. **AMENDMENTS AND OTHER DATES:**
Original Submission - 11/4/98
FDA Refusal to File - 12/8/98
Resubmission - 1/28/99
Labeling Review - not satisfactory - 4/2/99
Bio Review - not satisfactory- 5/4/99

Novex Letter - Revised Patent Certification - 5/18/99

FDA Letter from Tim Ames - Date?
Bio amendment to Novex - 6/7/99
Apotex Patent Amendment - 6/8/99
Apotex letter - corrected information - 7/21/99

10. **PHARMACOLOGICAL CATEGORY**
Narcotic
Antagonist/Agonist

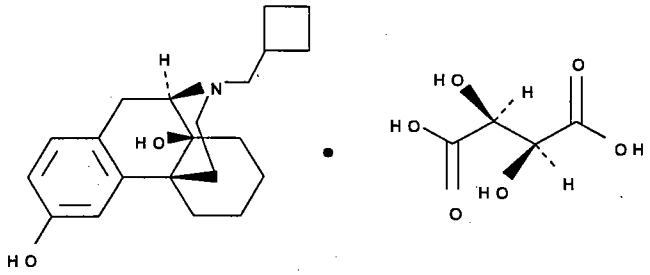
11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
NDA 19890 Bristol Myers Squibb
DMF #
DMF #
DMP #
DMF #

13. **DOSAGE FORM**
Metered Nasal Spray

14. **POTENCIES**
10 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**



Chemical Name:
(a) Morphinan-3,14-diol, 17-(cyclobutylmethyl),(-)-,[S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt);
(b) (-)-17(Cyclobutylmethyl)morphinan-3,14-diol [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt)

Molecular Formula: $C_{21}H_{29}NO_2.C_4H_6O_6$
M.W.: 477.55
CAS 58786-99-5

16. **RECORDS AND REPORTS**
4/2/99 - Labeling Review #1, A. Vezza.

5/4/99 - Bioequivalence Review #1, M. Markary.

17. **COMMENTS**

EER requested 2/26/99 - Results Pending
Labeling Review - Not Satisfactory - 4/2/99
Bio Review - Not Satisfactory- 5/4/99

This application represents the first generic for this drug product.

18. **CONCLUSIONS AND RECOMMENDATIONS**

Not Approvable - Major

19. **REVIEWER:** Tao-Chin L. Wang **DATE COMPLETED:** 8/5/99

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confidential commercial

information from

CHEMISTRY REVIEW #1

4.6 to 5.4. However, it is not consistent with the statement "to adjust the pH to ———" in the labeling insert as noted in the labeling review. Please clarify.

Sincerely yours,

9/7/99

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-499
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/TCLWang/8.5.99 T.-C.L. Wang 8/24/99 TCLW 9/7/99

HFD-647/GJSmith/8/20/99 9/2/99

HFD-617/MAnderson/8/20/99 Mark Anderson 9/2/99

F/T by pah/8/24/99
75499R01.RTW/V:\Firmsnz\Novex\Ltrs&Rev\75499R01.naf

CHEMISTRY REVIEW - NOT APPROVABLE - MAJOR

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

---

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-499

3. NAME AND ADDRESS OF APPLICANT

Novex Pharma
380 Eligin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

U.S. Agent:
Apotex Corp.
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061
Attention: Marcy MacDonald
Associated Director, Regulatory Affair

4. LEGAL BASIS FOR SUBMISSION

The reference listed drug is Stadol® NS™ (10 mg/mL Butorphanol Tartrate), Manufactured by Bristol Myers Squibb (NDA 19-890). U.S. Patent Number 4464378, University of Kentucky Research foundation, expiring August 7, 2001.

There is no unexpired exclusivity for this product. The firm filed a paragraph IV patent certification, in accordance with 21 CFR 314.94 (a) (12)(I)(A)(4) and Section 505 (j)(2)(A)(vii)(IV) of the Act.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Butorphanol Tartrate
Nasal Spray

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

11/4/98 -	Original Submission
1/28/99 -	Resubmission
5/18/99 -	Revised Patent Certification
6/8/99 -	Apotex Patent Amendment

7/21/99 - Apotex letter - corrected information
6/29/00 - Response to Deficiency Letter
8/21/00 - Bioequivalence Amendment
8/21/00 - Minor Amendment to the response of 6/29

FDA:
12/8/98 - Refusal to File
6/7/99 - Bio Deficiency Letter to Novex
9/9/99 - Deficiency Letter

10. **PHARMACOLOGICAL CATEGORY**
Narcotic
Antagonist/Agonist

11. **Rx or OTC**
Rx

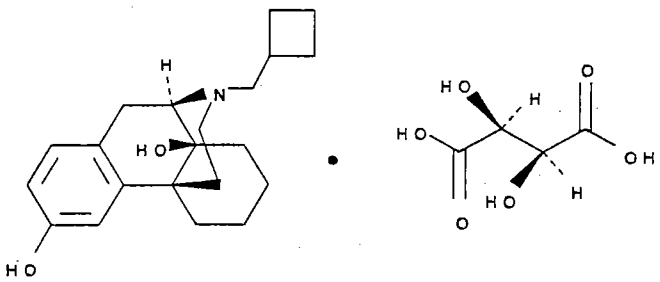
12. **RELATED IND/NDA/DMF(s)**
NDA 19890 Bristol Myers Squibb
DMF #
DMP #
DMF #
DMF #

13. **DOSAGE FORM**
Metered Nasal Spray

14. **POTENCIES**
10 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**

Butorphanol Tartrate



Chemical Name:
(a) Morphinan-3,14-diol, 17-(cyclobutylmethyl),(-)-,[S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt);

(b) (-)-17(Cyclobutylmethyl)morphinan-3,14-diol [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt)

Molecular Formula: $C_{21}H_{29}NO_2.C_4H_6O_6$
M.W.: 477.55
CAS 58786-99-5

16. RECORDS AND REPORTS

4/2/99 - Labeling Review #1, not satisfactory.
5/4/99 - Bioequivalence Review #1, not satisfactory.
7/7/00 - Labeling Review #2, not satisfactory.

17. COMMENTS

EER request was revised on 11/20/00, and the result is pending.
Labeling Review is not satisfactory, 7/7/00.
Bio Amendment, submitted on 8/21/2000, is under review.
DMF # ——— is inadequate, 11/16/00.
Revisions in Container, Laboratory Controls, and Stability are requested.

This application represents the first generic for this drug product.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable - Major

19. REVIEWER: Tao-Chin L. Wang

DATE COMPLETED: 11/17/00

Redacted 31 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA 75-499
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Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/TCLWang/11/17/00 For Mahboob Sarwar: 12,20,00

HFD-647/GJSmith/ 12/20/00

HFD-617/JMin/ 12/20/00

75499R02.RTW/V:\Firmsnz\Novex\Ltrs&Rev\75499R02.RTW

F/T

CHEMISTRY REVIEW - NOT APPROVABLE - MAJOR

1. **CHEMISTRY REVIEW NO.** 3

2. **ANDA #** 75-499

3. **NAME AND ADDRESS OF APPLICANT**

Novex Pharma
380 Eligin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

U.S. Agent:
Apotex Corp.
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061
Attention: Marcy MacDonald
Associated Director, Regulatory Affair
Tel: 847-573-9999
Fax: 847-573-1001

4. **LEGAL BASIS FOR SUBMISSION**

The reference listed drug is Stadol® NS™ (10 mg/mL Butorphanol Tartrate), Manufactured by Bristol Myers Squibb (NDA 19-890). U.S. Patent Number 4464378, University of Kentucky Research foundation, expiring August 7, 2001.

There is no unexpired exclusivity for this product. The paragraph IV patent certification initially filed has been revised to Paragraph III certification, 4/18/01 Correspondence.

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Butorphanol Tartrate
Nasal Spray

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

Firm:

11/4/98 -	Original Submission
1/28/99 -	Resubmission
5/18/99 -	Revised Patent Certification
6/8/99 -	Apotex Patent Amendment

7/21/99 - Apotex letter - corrected information
6/29/00 - Major Amendment
8/21/00 - Bioequivalence Amendment
8/21/00 - Minor Amendment
4/18/01 - New Correspondence
5/23/01 - Major Amendment
11/14/01 - T-con Amendment

FDA:
12/8/98 - Refusal to File
6/7/99 - Bio Deficiency Letter to Novex
9/9/99 - Deficiency Letter
12/22/00 - Deficiency Letter
11/5/01 - T-con

10. **PHARMACOLOGICAL CATEGORY**
Narcotic Antagonist/Agonist

11. **Rx or OTC**
Rx

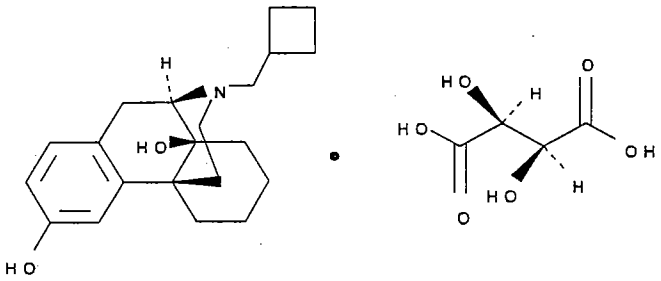
12. **RELATED IND/NDA/DMF(s)**
NDA 19890 Bristol Myers Squibb
DMF #
DMF #
DMP #
DMF #
DMF #

13. **DOSAGE FORM**
Metered Nasal Spray

14. **POTENCIES**
10 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**

Butorphanol Tartrate
$C_{21}H_{29}NO_2.C_4H_6O_6$; M.W.: 477.55



Chemical Name:

(a) Morphinan-3,14-diol, 17-(cyclobutylmethyl),(-)-,[S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt);

(b) (-)-17(Cyclobutylmethyl)morphinan-3,14-diol [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt)

CAS 58786-99-5

16. **RECORDS AND REPORTS**

4/2/99 -	Labeling Review
5/4/99 -	Bioequivalence Review #1
9/7/99 -	Chemistry Review #1
7/7/00 -	Labeling Review
12/20/00 -	Chemistry Review #2
6/18/01 -	Labeling Review

17. **COMMENTS**

Acceptable EIR was issued from the Office of Compliance on 3/19/01.

Labeling Review is pending.

Bioequivalence studies are found not satisfactory, 4/6/01.

DMF #[redacted]is adequate, 9/4/01.

Drug substance is compendial. Drug product is not compendial. Method validation was submitted to Northeast Regional Laboratory on 1/4/2001. Butorphanol Tartrate Assay, Benzethonium Chloride Assay, Degradation Products, and Assay of Butorphanol Tartrate per Spray (Uniformity of Dosage Units) testing methods were found acceptable with minor revision, 7/3/01. However, Northeast Regional Laboratory does not have adequate equipment to validate the testing method for Spray Pattern and Spray Droplet Size Distribution.

18. **CONCLUSIONS AND RECOMMENDATIONS**

Approvable - pending Bio and Labeling

19. **REVIEWER:** Tao-Chin L. Wang **DATE COMPLETED:** 10/19/01

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confidential commercial

information from

CHEMISTRY REVIEW #3

37. **DMF CHECKLIST FOR ANDA #75-499 REVIEW # 3**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
	II/	3	Adequate	9/4/01

Comments: DMF as amended is adequate per review by T.-C. L. Wang.

III/

Comments: 4

III/

Comments: 4

III/

Comments: 4

Comments:

Comments:

Comments:

Comments:

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under "Comments").

Tsae-Chi L. Wang 11/27/01
Reviewer Signature Date

38. Chemistry Comments to be Provided to the Applicant

ANDA 75-499 Applicant Novex Pharma

Drug Product Butorphanol Tartrate Nasal Spray

The deficiency presented below represent a Minor deficiency.

The Division of Chemistry has no further questions at this time. We refer to the facsimile dated April 30, 2001 regarding deficiencies in the bioequivalency section of your application. These deficiencies must be answered satisfactorily before the application can be approved. Please note that any changes made to the chemistry, manufacturing and controls section of your application as a result of outstanding bioequivalency deficiencies must be submitted and could result in the response being considered a MAJOR Amendment.

Sincerely yours,

11/29/01

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-499
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/TCLWang/10/19/01, 11/20/01 TCLWang 11/27/01

HFD-647/GJSmith/11/21/01 11/20/01

HFD-617/JMin/11/27/01 11/28/01

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F/T

CHEMISTRY REVIEW - APPROVABLE - Pending Bio and Labeling

APPEARS THIS WAY
ON ORIGINAL

1. **CHEMISTRY REVIEW NO.** 4

2. **ANDA #** 75-499

3. **NAME AND ADDRESS OF APPLICANT**

Novex Pharma
380 Eligin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

U.S. Agent:
Apotex Corp.
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061
Attention: Marcy MacDonald
Associated Director, Regulatory Affair
Tel: 847-573-9999
Fax: 847-573-1001

4. **LEGAL BASIS FOR SUBMISSION**

The reference listed drug is Stadol® NS™ (10 mg/mL Butorphanol Tartrate), Manufactured by Bristol Myers Squibb (NDA 19-890). U.S. Patent Number 4464378, University of Kentucky Research foundation, expiring August 7, 2001.

There is no unexpired exclusivity for this product. The paragraph IV patent certification initially filed has been revised to Paragraph III certification, 4/18/01 Correspondence.

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Butorphanol Tartrate
Nasal Spray

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

Firm:

11/4/98 -	Original Submission
1/28/99 -	Resubmission
5/18/99 -	Revised Patent Certification
6/8/99 -	Apotex Patent Amendment

7/21/99 - Apotex letter - corrected information
6/29/00 - Major Amendment
8/21/00 - Minor Amendment
8/22/00 - Major Amendment
10/31/00 - Bio Amendment
1/15/01 - Bio Amendment
4/18/01 - New Correspondence
5/25/01 - Major Amendment
11/16/01 - T-con Amendment
11/29/01 - Minor Amendment
12/3/01 - Minor Amendment
1/18/02 - Fax Amendment

FDA:
12/8/98 - Refusal to File
6/7/99 - Bio Deficiency Letter to Novex
9/9/99 - Deficiency Letter
12/22/00 - Deficiency Letter
11/5/01 - T-con
11/29/01 - Deficiency Letter
5/9/01 - Bio Deficiency Letter to Novex

10. **PHARMACOLOGICAL CATEGORY**
Narcotic
Antagonist/Agonist

11. **Rx or OTC**
Rx

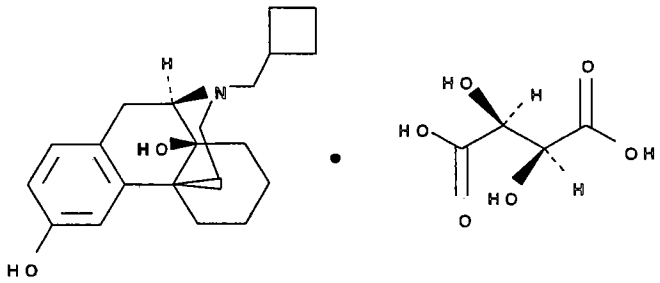
12. **RELATED IND/NDA/DMF(s)**
NDA 19890 Bristol Myers Squibb
DMF #
DMF #
DMP #
DMF #
DMF #

13. **DOSAGE FORM**
Metered Nasal Spray

14. **POTENCIES**
10 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**

Butorphanol Tartrate
$C_{21}H_{29}NO_2 . C_4H_6O_6$; M.W.: 477.55



Chemical Name:
(a) Morphinan-3,14-diol, 17-(cyclobutylmethyl),(-)-,[S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt);
(b) (-)-17(Cyclobutylmethyl)morphinan-3,14-diol [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt)

CAS 58786-99-5

16. **RECORDS AND REPORTS**

4/2/99 -	Labeling Review
5/4/99 -	Bioequivalence Review #1
9/7/99 -	Chemistry Review #1
7/7/00 -	Labeling Review
12/20/00 -	Chemistry Review #2
6/18/01 -	Labeling Review
1/17/02 -	Bioequivalence Review #1
2/7/02 -	Labeling Review

17. **COMMENTS**

Acceptable EIR was issued from the Office of Compliance on 3/19/01.

Labeling is acceptable, 4/1/02.

Bioequivalence is deficient, 5/9/02.

DMF # [redacted] is adequate per review by T. Hendricks, 2/02.

Drug substance is compendial. Drug product is not compendial. Method validation was submitted to Northeast Regional Laboratory on 1/4/2001. Butorphanol Tartrate Assay, Benzethonium Chloride Assay, Degradation Products, and Assay of Butorphanol Tartrate per Spray (Uniformity of Dosage Units) testing methods were found acceptable with minor revision, 7/3/01. However, Northeast Regional Laboratory does not have adequate equipment to validate the

testing method for Spray Pattern and Spray Droplet Size Distribution.

18. **CONCLUSIONS AND RECOMMENDATIONS**
Approvable - pending Bio and ~~Labeling~~

19. **REVIEWER:** Tao-Chin L. Wang **DATE COMPLETED:** 2/14/02

APPEARS THIS WAY
ON ORIGINAL

Redacted 21 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW #4

34. **BIOEQUIVALENCY STATUS**

Bioequivalence is deficient, 5/9/02.

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:**

The firm claims categorical exclusion per 21CFR 25.24(c)(1) from the requirement to file an Environmental Impact Assessment Statement for the production of the proposed drug product. A signed certification of compliance with federal, state, and local environmental regulations is provided.

36. **ORDER OF REVIEW:**

The application submission(s) covered by this review was taken in the date order of receipt Yes X

No _____

If no, explain reason(s) below:

SPOT? Yes _____ No X

If yes, complete a SPOT form.

APPEARS THIS WAY
ON ORIGINAL

37. **DMF CHECKLIST FOR ANDA #75-499 REVIEW # 4**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/[redacted]	3	Adequate	2/02

Comments: DMF # [redacted] is adequate per review by T. Hendricks, 2/02.

[redacted] III/[redacted]

Comments: 4

[redacted] III/[redacted]

Comments: 4

[redacted] III/[redacted]

Comments: 4

Comments:

Comments:

Comments:

Comments:

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under "Comments").

Jiao-Chun Z. Wang 5/16/02
Reviewer Signature Date

38. Chemistry Comments to be Provided to the Applicant

ANDA 75-499 Applicant: Novex Pharma

Drug Product: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The deficiencies presented below represent MINOR deficiencies.

The Division of Chemistry has no further questions at this time. We refer to the facsimile dated, May 9, 2002 regarding deficiencies in the bioequivalence section of your application. These deficiencies must be answered satisfactorily before the application can be approved. Please note that any changes made to the chemistry, manufacturing and controls section of your application as a result of outstanding bioequivalence deficiencies must be submitted and could result in the response being considered a MAJOR Amendment.

Sincerely yours,

5/20/02

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-499
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/TCLWang/2/14/02 TCL Wang 5/16/02

HFD-647/GJSmith/2/26/02 5/17/02

HFD-617/JMin/3/2/02 5/17/02

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F/T by jsm/5/16/02

CHEMISTRY REVIEW - Minor - Pending Bio

APPEARS THIS WAY
ON ORIGINAL

1. **CHEMISTRY REVIEW NO.** 5

2. **ANDA #** 75-499

3. **NAME AND ADDRESS OF APPLICANT**

Novex Pharma
380 Eligin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

U.S. Agent:
Apotex Corp.
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061
Attention: Marcy MacDonald
Associated Director, Regulatory Affair
Tel: 847-573-9999
Fax: 847-573-1001

4. **LEGAL BASIS FOR SUBMISSION**

The reference listed drug is Stadol® NS™ (10 mg/mL Butorphanol Tartrate), Manufactured by Bristol Myers Squibb (NDA 19-890). U.S. Patent Number 4464378, University of Kentucky Research foundation, expiring August 7, 2001.

There is no unexpired exclusivity for this product. The paragraph IV patent certification initially filed has been revised to Paragraph III certification, 4/18/01 Correspondence.

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Butorphanol Tartrate
Nasal Spray

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

Firm:

11/4/98 -	Original Submission
1/28/99 -	Resubmission
5/18/99 -	Revised Patent Certification
6/8/99 -	Apotex Patent Amendment

7/21/99 - Apotex letter - corrected information
6/29/00 - Major Amendment
8/21/00 - Minor Amendment
8/22/00 - Major Amendment
10/31/00 - Bio Amendment
1/15/01 - Bio Amendment
4/18/01 - New Correspondence
5/25/01 - Major Amendment
11/16/01 - T-con Amendment
11/29/01 - Minor Amendment
12/3/01 - Minor Amendment
1/18/02 - Fax Amendment
8/9/02 - Bio Amendment
8/13/02 - Minor Amendment

FDA:
12/8/98 - Refusal to File
6/7/99 - Bio Deficiency Letter to Novex
9/9/99 - Deficiency Letter
12/22/00 - Deficiency Letter
11/5/01 - T-con
11/29/01 - Deficiency Letter
5/9/01 - Bio Deficiency Letter to Novex
5/20/02 - Deficiency Letter

10. **PHARMACOLOGICAL CATEGORY**
Narcotic
Antagonist/Agonist

11. **Rx or OTC**
Rx

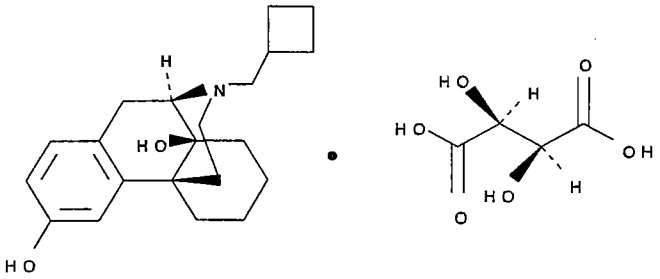
12. **RELATED IND/NDA/DMF(s)**
NDA 19890 Bristol Myers Squibb
DMF #
DMF #
DMP #
DMF #
DMF #

13. **DOSAGE FORM**
Metered Nasal Spray

14. **POTENCIES**
10 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**

Butorphanol Tartrate
$C_{21}H_{29}NO_2 . C_4H_6O_6$; M.W.: 477.55



Chemical Name:
(a) Morphinan-3,14-diol, 17-(cyclobutylmethyl),(-)-,[S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt);
(b) (-)-17(Cyclobutylmethyl)morphinan-3,14-diol [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt)

CAS 58786-99-5

16. **RECORDS AND REPORTS**

4/2/99 -	Labeling Review
5/4/99 -	Bioequivalence Review
9/7/99 -	Chemistry Review #1
7/7/00 -	Labeling Review
12/20/00 -	Chemistry Review #2
6/18/01 -	Labeling Review
11/28/01 -	Chemistry Review #3
1/17/02 -	Bioequivalence Review
2/7/02 -	Labeling Review
5/17/02 -	Chemistry Review #4
9/6/02 -	Bioequivalence Review

17. **COMMENTS**

Acceptable EIR was issued from the Office of Compliance on 3/19/01.

Labeling is acceptable, 4/1/02.

Bioequivalence is acceptable, 9/6/02.

DMF # [redacted] is adequate, 11/15/02.

Drug substance is compendial. Drug product is not compendial. Method validation was submitted to Northeast Regional Laboratory on 1/4/2001. Butorphanol Tartrate Assay, Benzethonium Chloride Assay, Degradation Products, and Assay of Butorphanol Tartrate per Spray (Uniformity of Dosage Units) testing methods were found acceptable with

minor revision, 7/3/01. The firm has responded satisfactorily to the revision requested. However, Northeast Regional Laboratory does not have adequate equipment to validate the testing method for Spray Pattern and Spray Droplet Size Distribution.

18. **CONCLUSIONS AND RECOMMENDATIONS**
Approvable

19. **REVIEWER:** Tao-Chin L. Wang

DATE COMPLETED: 11/19/02

APPEARS THIS WAY
ON ORIGINAL

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information from

CHEMISTRY REVIEW #5

cc: ANDA 75-499
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/TCLWang/11/19/02 TCLWang 11/25/02

HFD-647/GJSmith/11/20/02 11/25/02

HFD-617/THinchliffe/11/20/02 11/25/02

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F/T by rad11/21/02

CHEMISTRY REVIEW - Approvable

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

BIOEQUIVALENCE REVIEWS

Butorphanol Tartrate
Nasal Spray, 10 mg/mL
ANDA #75-499
Reviewer: Moheb H. Makary
W 75499sd.199

Novex Pharma
Richmond Hill, Ontario
Submission Date:
January 25, 1999

Review of In Vitro Data

I. Objective:

The firm has submitted comparative formulation data of its proposed test product and the reference listed drug Stadol[R] Nasal Spray, 10 mg/mL. The firm conducted comparative *in vitro* testing on unit dose, spray pattern, plum geometry, droplet size distribution (cascade impactor and laser diffraction), priming and tail off sprays.

II. Background:

Butorphanol Tartrate Nasal Spray, 10 mg/mL, is indicated for the management of pain when the use of an opioid analgesic is appropriate. The reference listed drug is Stadol®, nasal solution (Bristol-Myers), which is a combination of formulation and a manual metering device. It is marketed as a solution provided in 2.5 mL fill bottles; one bottle delivers 14-15 sprays (100 µL/spray, 1 mg/spray). The drug exerts *in vivo* effect(s) through the systemic circulation following absorption from the nasal cavity.

III. Formulations: (Not to be released under FOI)

Table I

Ingredient	Reference*	Test
	g/L	
Butorphanol Tartrate	10 g	10 g
Sodium Chloride	———	———
Citric Acid	———	———
Benzethonium Chloride	———	———
Sodium Hydroxide	Adjust pH	Adjust pH
Hydrochloric Acid	Adjust pH	-----
Water, Purified	Qs	Qs

*Based on the FDA COMIS data base, the amount of sodium hydroxide in the reference product is not specified. COMIS did not specify the pH.

III. Comments:

1. Comparative formulations of the reference and the proposed test product are given in Table I. Based on the data submitted by the sponsor, composition of the proposed test product is qualitatively and quantitatively the same as in the reference product.

2. A summary of the firm's comparative *in vitro* testing on unit dose, spray pattern, plume geometry, droplet size distribution (cascade impactor and laser diffraction), priming and tail off sprays is attached. The *in vitro* testing is incomplete. Reviewer's comments on each *in vitro* test are as follows:

2.1 Unit dose and uniformity of unit dose

Consistent with the Potency Test described in the 27 June 1989 Division of Bioequivalence Guidance for the "In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)", this test should be performed at beginning, middle, and end of use life of the product after product priming.

For Butorphanol Tartrate Nasal Spray, a dose is one spray (1 mg). The amount of drug per single spray (not the mean of two or more consecutive sprays) should be determined using a validated stability-indicating biochemical/chromatographic assay. In addition to the chemical assay of drug per spray, measurement of spray weight is also requested. The firm should clarify the unit weight in Figure 5.

2.2 Spray Pattern

Spray patterns should be determined at three distances from the TLC plate at beginning and end life sectors. Spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug-specific reagent. A drug-specific reagent will not develop color when tested

with placebo. Photographs of spray patterns, in color if appropriate, should be analyzed to measure the shortest (D_{min}) and widest (D_{max}) diameters. Reported data should include values of D_{min}, D_{max} and ovality ratio (D_{max}/D_{min}), along with photographs and markings indicating D_{min} and D_{max}.

2.3 Plume Geometry

Plume geometry describes two side views, at a 90^0 angle to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. The firm should provide plume geometry based on high speed photography. Plume geometry may be performed only at beginning of use life. Plumes should be characterized at three or more delay times after actuation. These times should be chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time. Photographs of spray plumes should be used to measure plume length, plume width, and plume (spray cone) angle. The firm is requested to provide all photographs and data characterizing plume dimensions including scaling information to indicate actual size.

2.4 Droplet size distribution

a. Laser Diffraction: Droplet size distribution by laser diffraction (e.g. ———————, should be determined at the beginning, middle, and end of use life of the product. Measurements should be made at three distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. Data should be reported in the form of D_{10}, D_{50}, D_{90} and SPAN $[(D_{90}-D_{10}/D_{50})]$. Data should be reported based on mass (volume). All instrument/computer printouts should also be submitted, including cumulative percent undersize tables and histograms of particle size distribution. Obscuration should be reported for each run, along with the instrument manufacturer's recommended obscuration ranges.

b. Cascade impaction: The cascade impactor characterizes particles in a smaller size range than the expected range for aqueous nasal sprays. However, it is useful as to assure that there is not an excess mass of "fines" in the test product relative to the RLD. Cascade impactor

(———, data should account for mass balance and be reported in the following groups:

Group-1: From valve stem and actuator up to top stage (stage zero).
Group-2: One stage below the top stage.
Group-3: Everything from 2nd stage through the filter.

Because the purpose of the cascade impactor for the aqueous nasal sprays is to characterize fines only, not to provide a particle size distribution, the firm is requested to provide cascade impactor studies only at the beginning and end of canister through-life testing.

c. Other methods: The firm may, if it wishes, provide comparative data by additional methods such as time-of-flight laser.

2.5 PRIMING, LOSS OF PRIME, AND TAIL OFF

Priming: The reference listed drug's patient package insert indicates that up to 7-8 actuations are required to prime. The sponsor should submit data to support the statement that the test product requires no more actuations to prime than does the reference product.

Loss of Prime: The reference listed drug's patient package insert indicates that it must be primed by wasting 1-2 sprays, if not used for 48 hours or longer. The sponsor should submit comparative data for similar performance characteristics of the test and reference products.

Tail Off: Evidence for comparable tail off characteristics should be submitted.

Priming, loss of prime and tail off data should be based on the amount of drug per actuation using a biochemical/chromatographic assay. Because the product is labeled to deliver only 14-15 doses, the firm may combine determination of priming, uniformity of unit dose and tail off in single studies in which drug content in all successive individual actuations (from the first unprimed dose to depletion) is quantitated.

2.6 For all the above comparative *in vitro* tests

a. Pumps should be actuated mechanically to increase reproducibility.

b. No fewer than 10 units (i.e., 10 bottles and associated delivery devices) each of the test and reference products should be tested in a blinded manner.

c. For all in vitro tests, the firm may wish to submit data from three batches of the reference product, and three batches of the test product. Batch records for all batches of the test product should be submitted. For the test product, the firm may also submit data from a single batch of the solution with a split fill into three equal size sublots, with each sublot prepared from different batches of test product devices (pump and actuator).

d. SOP's for all tests effective at the time of testing should be submitted. SOP's should describe the mechanical actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s). Blinding must not interfere with pump performance.

e. Raw data for all tests should be submitted in the form of paper copies as well as electronic files (Excel 5.0 spread sheets).

f. For tests performed at the beginning (B), middle (M), and end (E) or B and E of use life sectors, equivalence will be assessed at each sector.

3. Metering Devices

The device and the formulation are integral components of a nasal spray. To support sameness of test and reference devices, the firm should provide to the extent possible a side-by-side comparison of the pumps (including diptube length) and actuators used in the test and reference products. This information should include the manufacturer, model numbers of the pumps and actuators, and model numbers of actuator inserts and the overcaps. Technical drawings with dimensions should also be submitted for both the test and reference products, if available.

4. The firm may wish to consider conducting an acceptable *in vivo* bioequivalence study as a condition for approval of its test product instead of submitting the above mentioned comparative *in vitro* tests.

V. Recommendation:

The *in vitro* performance testing conducted by Novex Pharma, on its Butorphanol Tartrate Nasal Spray Pump, 10 mg/mL, lot #8X190, is incomplete for the reasons mentioned in comments 2.1-2.6.

The firm should be informed of the comments and recommendation.

Moheb H. Makary

Moheb H. Makary, Ph.D. Date: 5/4/99
Review Branch III
Division of Bioequivalence

RD INITIALLED BDAVIT BMD 4/30/99
FT INITIALLED BDAVIT Barbara M Davit Date: 5/4/99

Concur: for Dale P. Conner Date: 5/26/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 3-11-99, 4-22-99, 5-4-99, 75499dw.199
cc: ANDA #75-499, original, HFD-658(Makary), Drug File, Division File.

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-499 APPLICANT: Novex Pharma

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has the following comments:

1.1 Unit dose and uniformity of unit dose

Consistent with the Potency Test described in the 27 June 1989 Division of Bioequivalence Guidance for the "In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)", this test should be performed at beginning, middle, and end of use life of the product after product priming.

For Butorphanol Tartrate Nasal Spray, a dose is one spray (1 mg). The amount of drug per single spray (not the mean of two or more consecutive sprays) should be determined using a validated stability-indicating biochemical/chromatographic assay. In addition to the chemical assay of drug per spray, measurement of spray weight is also requested. Please clarify the unit weight in Figure 5.

1.2 Spray Pattern

Spray patterns should be determined at three distances from the TLC plate at beginning and end life sectors. Spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug-specific reagent. A drug-specific reagent will not develop color when tested with placebo. Photographs of spray patterns, in color if appropriate, should be analyzed to measure the shortest (D_{min}) and widest (D_{max}) diameters. Reported data should include values of D_{min}, D_{max} and ovality ratio (D_{max}/D_{min}), along with photographs and markings indicating D_{min} and D_{max}.

1.3 Plume Geometry

Plume geometry describes two side views, at a 90^0 angle to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. Please provide plume geometry based on high speed photography. Plume geometry may be performed only at beginning of use life. Plumes should be characterized at three or more delay times after actuation. These times should be chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time. Photographs of spray plumes should be used to measure plume length, plume width, and plume (spray cone) angle. Please provide all photographs and data characterizing plume dimensions including scaling information to indicate actual size.

1.4 Droplet size distribution

a. Laser Diffraction: Droplet size distribution by laser diffraction (e.g. ————————) should be determined at the beginning, middle, and end of use life of the product. Measurements should be made at three distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. Please report the data in the form of D_{10}, D_{50}, D_{90} and SPAN $[(D_{90}-D_{10}/D_{50})]$. Please report the data based on mass (volume). Please submit all instrument/computer printouts, including cumulative percent undersize tables and histograms of particle size distribution. Obscuration should be reported for each run, along with the instrument manufacturer's recommended obscuration ranges.

b. Cascade impaction: The cascade impactor characterizes particles in a smaller size range than the expected range for aqueous nasal sprays. However, it is useful as to assure that there is not an excess mass of "fines" in the test product relative to the RLD. Cascade impactor (————) data should account for mass balance and be reported in the following groups:

Group-1: From valve stem and actuator up to top stage (stage zero).
Group-2: One stage below the top stage.
Group-3: Everything from 2nd stage through the filter.

Because the purpose of the cascade impactor for the aqueous nasal sprays is to characterize fines only, not to provide a particle size distribution, please provide cascade impactor studies only at the beginning and end of canister through-life testing.

c. Other methods: You may wish to provide comparative data by additional methods such as time-of-flight laser.

1.5 PRIMING, LOSS OF PRIME, AND TAIL OFF

Priming: The reference listed drug's patient package insert indicates that up to 7-8 actuations are required to prime. Please submit data to support the statement that the test product requires no more actuations to prime than does the reference product.

Loss of Prime: The reference listed drug's patient package insert indicates that it must be primed by wasting 1-2 sprays, if not used for 48 hours or longer. Please submit comparative data for similar performance characteristics of the test and reference products.

Tail Off: Please submit evidence for comparable tail off characteristics.

Priming, loss of prime and tail off data should be based on the amount of drug per actuation using a biochemical/chromatographic assay. Because the product is labeled to deliver only 14-15 doses, you may combine determination of priming, uniformity of unit dose and tail off in single studies in which drug content in all successive individual actuations (from the first unprimed dose to depletion) is quantitated.

1.6 For all the above comparative *in vitro* tests

a. Pumps should be actuated mechanically to increase reproducibility.

b. No fewer than 10 units (i.e., 10 bottles and associated delivery devices) each of the test and reference products should be tested in a blinded manner.

c. For all *in vitro* tests, you may wish to submit data from three batches of the reference product, and three batches of the test product. However, for the test product you may submit data from a single batch of the solution with a split fill into three equal size sublots, with each sublot prepared from different batches of test product devices (pump and actuator). Batch records for all batches of the test product should be submitted.

d. Please submit SOP's for all tests effective at the time of testing. SOP's should describe the mechanical actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s). Blinding must not interfere with pump performance.

e. Please submit raw data for all tests in the form of paper copies as well as electronic files (Excel 5.0 spread sheets).

f. For tests performed at the beginning (B), middle (M), and end (E) or B and E of use life sectors, equivalence will be assessed at each sector.

2. Metering Devices

The device and the formulation are integral components of a nasal spray. To support sameness of test and reference devices, please provide to the extent possible a side-by-side comparison of the pumps (including diptube length) and actuators used in the test and reference products. This information includes the manufacturer, model numbers of the pumps and actuators, and model numbers of actuator inserts and the overcaps. Please submit technical drawings with dimensions for both the test and reference products, if available.

3. You may wish to consider conducting an acceptable *in vivo* bioequivalence study as a condition for approval of the test product instead of submitting the above mentioned comparative *in vitro* tests. In such case the *in vivo* pharmacokinetic data will be used for evaluation of bioequivalence.

Sincerely yours,

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #75-499
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-658/Reviewer M. Makary
HFD-658/Bio Team Leader B. davit BMD
HFD-617/Project Manager 5/27/99
HFD-650/Dale Conner for 5/26/99

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BIOEQUIVALENCY-DEFICIENCIES Submission Date: January 25, 1999

OK BMD 3/4/99

1. In-Vitro study — All Strengths 10 mg/mL — **Outcome: IC**

Outcome Decisions:
IC - Incomplete

APPEARS THIS WAY
ON ORIGINAL

Butorphanol Tartrate
Nasal Spray, 10 mg/mL
ANDA #75-499
Reviewer: Moheb H. Makary
W 75499sd.800

Novex Pharma
Richmond Hill, Ontario
Submission Dates:
August ~~22~~ 21, 2000
June 29, 2000
October ~~30~~ 31, 2000
January ~~11~~ 15, 2001

Review of Amendments

I. Objective:

The firm has replied to the comments made by the Division of Bioequivalence (DBE) its letter of January 25, 1999 submission (*In Vitro* Performance Studies on Butorphanol Tartrate, Nasal Spray, 10 mg/mL).

II. Review of application:

Formulation:

Composition of the test product is quantitatively and qualitatively the same as the reference listed drug (see earlier review dated January 25, 1999).

Drug Products:

Test: Novex Pharma's Butorphanol Nasal Spray, 10 mg/mL, consisted of one lot of the drug solution formulation (Lot #8X190, Lot size ——— divided into three sublots using three separate batches of pumps (Novex Pharma QC Nos. 5325, 4406 and 5284).

Reference: Bristol-Myers Squibb's Stadol NS^R, 10 mg/mL; Lots 9F15910 Exp. 6/2001, 9F10028 Exp. 5/2001 and M8K050B Exp. 12/2000.

Comparability of Spray Devices:

——————— developed and provided to Novex Pharma a nasal spray pump, which was almost identical to that of the innovator product. ——————— also supplies the pumps used for Stadol NS^R. A physical comparison between the Novex Pharma pump and Stadol NS^R pump is shown in Vol. 3.1, page 10, a copy of the drawing for Novex Pharma's pump (Attachment No. 12, Vol. 3.8) also is attached herewith.

Procedures and Information Applicable to All Tests:

All actuations of the nasal spray products were done using a mechanical actuator to actuate the nasal sprays in a reproducible manner. The mechanical actuator used was a proprietary unit designed by ———————, for nasal spray actuation. The force required for actuation of the nasal sprays was specified at 4.5 ± 0.5 kg.

DBE Comment #I

Unit dose and uniformity of unit dose

Consistent with the Potency Test described in the 27 June 1989 Division of Bioequivalence Guidance for the "In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)", this test should be performed at beginning, middle, and end of use life of the product after product priming.

For Butorphanol Tartrate Nasal Spray, a dose is one spray (1 mg). The amount of drug per single spray (not the mean of two or more consecutive sprays) should be determined using a validated stability-indicating biochemical/chromatographic assay. In addition to the chemical assay of drug per spray, measurement of spray weight is also requested. The firm was asked to clarify the unit weight in Figure 5.

Firm's Response

Novex Pharma submitted data for the above-mentioned testing. The firm performed the uniformity of unit dose test using a stability-indicating method [Test Method No. TM-1182, Assay of Butorphanol Tartrate per Spray in Butorphanol Tartrate Nasal Spray (10 mg/mL), Vol 3.8, page 2909]. The quantity of the drug is based on each single spray in order to be consistent with dosing requirements. Since the labeled number of full medication doses per bottle is 14 sprays, the unit dose test was carried out on the entire bottle to determine the priming, prime retention and tail-off characteristics. It should be noted that due to the limited availability of the reference product (Stadol^{R} NS) at the time of purchase, two sprays from each bottle, *spray #9 and #22* (representing the beginning and end sprays of the product), were used to determine droplet size by cascade impaction.

For each test, ten (10) units from each of the three sub-lots of the test product and each of the three lots of the reference product were tested. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were tested.

The weight of individual sprays was determined by weighing bottles before and after each spray collection, and the amount of drug per spray was determined by a validated HPLC analysis (LOQ= —————).

Content uniformity summary results were reported at the beginning (actuation 8), middle (actuation 15) and end of unit life (actuation 21). The following table provides a summary based on the reviewer's calculations.

Table I

UNIT DOSE DATA

			Variability (%CV)			TEST/REF		
						Arith Mean	Geo Mean	
PROD.	SECTOR	Mean*	Within-Lot	Between-lot	Total			p
		(N = 30)	(N=10)	(N=3)	(N=30)	(N = 30)		
	BEG	111.88	1.7-2.6	1.9	2.6	1.03	1.03	0.0004
TEST	MID	112.38	1.4-3.8	2.2	3.2	1.03	1.03	0.0054
	END	112.90	1.6-3.7	1.7	2.9	1.03	1.03	0.0016
	BEG	108.21	1.0-3.1	2.0	3.1			
REF	MID	109.58	1.2-2.3	2.3	2.7			
	END	109.44	1.5-3.3	1.4	2.9			

** The mean unit dose data are expressed % of label claim based on arithmetic means. Outcome of the statistical analysis remains the same whether the data are expressed as % LC or amount spray.*

Comments on the Unit Dose Data

1. For Novex's Butorphanol Tartrate, the geometric mean values at actuations 8, 15 and 21 values are 3.0% higher, than the corresponding reference product values. The test and the reference products exhibited approximately same variability (%CV) with regard to the unit dose data. The test/ref ratios are within the 90-111% limits stipulated in the Draft Nasal BA/BE Guidance.

2. The quantity of the drug assayed is based on each single spray. A bottle delivers 14-15 sprays. The minimum and maximum values for the test product show that the delivered doses fall within 110.3-115.0% of the labeled dose. The draft guidance recommends that based on the 'first tier' of testing (10 units), not more than one unit be outside 80-120% of the label claim, and none should be outside the 75-125%, and mean values should not outside 85-115%.

3. Based on the mean values, there was no change in the unit dose determined at the beginning, middle and end sectors. Furthermore, the data did not show a particular trend in changes in variability between the three life sectors.

4. There is a good correlation between the quantity of the drug delivered per spray obtained by weight and that obtained by assay using an HPLC method.

5. Based on the data obtained, the test product is fully primed at the 4^{th} spray (see Table II). The loss of prime retention is determined on the 10^{th} spray by allowing the product to rest for a period of 48 hours, followed by collecting the next spray without priming. Based on the data submitted, the test and reference products have same prime retention characteristics.

6. Tail off is performed by assaying the end sprays until the weight of the spray reaches approximately 20% of its theoretical full weight and visual observation by the analyst indicates that there are very few droplets emitted by actuation. Data given in Table II indicate that the test product delivers the labeled numbers of doses and it's tail off is no more erratic than that of the reference product.

7. With respect to the unit weight in Figure 5 submitted previously (dated January 25, 1999), Novex Pharma made a typographical error in this figure included the Refusal to File Response dated January 28, 1999. The Unit weight in this figure should have been in grams, not milligrams. A replacement page for Figure 5 with the corrected unit weight (in grams) has been provided in Attachment No.3 (Volume 3.1) of this amendment.

8. Based on the foregoing, the firm response to the DBE comment on unit dose and content uniformity is acceptable.

DBE Comment II:

Droplet size distribution

a. Laser Diffraction: Droplet size distribution by laser diffraction (e.g. [redacted]) should be determined at the beginning, middle, and end of use life of the product. Measurements should be made at three distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. The firm was asked to report the data in the form of D_{10}, D_{50}, D_{90} and SPAN $[(D_{90}-D_{10}/D_{50})]$.

Firm's Response

Droplet size determination was performed on 10 units from each of the 3 unit lots of test and reference products. Each unit was tested at beginning, middle, and end sectors of unit life. At each sector of unit life, each unit was actuated at three distances relative to the [redacted] laser beam (3 cm, 4 cm, and 5 cm). At each distance, measurements were taken at different delay times. Based on the information submitted in the January 11, 2001 amendment the, the three delay times characterize three regions in the plume life based on % transmission:

Plume Region	Transmission Characteristic
Plume formation (Initial)	Drops
Fully formed plume (Intermediate)	Stable
Plume dissipation (End)	Rises

The three separate regions constitute the sampling points on which the droplet size distribution data are based. The delay times representing these regions vary with the actuation distances.

The firm submitted D10, D50, D90 and SPAN data. Bioequivalence evaluation is based on D50 and SPAN data. A summary of these data based on the reviewer's calculations is given in Table III.

Table III
Droplet Size Distribution (D50 Data) - Test Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo Mean(N=30)	p
		3	Initial	46.80	16.8-21.8	9.0	21.3	0.87	0.94	0.28
		3	Intermediate	45.80	15.8-49.0	6.6	13.5	1.09	1.11	0.12
		3	End	111.30	18.5-19.7	3.1	19.0	1.07	1.08	0.2
		4	Initial	47.70	23.4-27.8	3.3	25.2	1.00	1.05	0.94
	BEG	4	Intermediate	43.50	10.2-14.9	12.4	15.7	1.06	1.08	0.36
		4	End	95.30	33.8-34.2	4.7	32.9	1.06	1.06	0.56
		5	Initial	46.80	22.4-50.5	17.4	53.1	0.95	0.95	0.72
		5	Intermediate	40.70	11.1-15.2	6.2	10.9	0.99	1.01	0.88
		5	End	76.80	28.5-33.4	10.6	31.9	1.04	1.05	0.66
		3	Initial	50.80	9.8-18.4	18.6	23.9	1.03	1.10	0.76
		3	Intermediate	47.60	9.3-28.0	14.0	23.6	1.13	1.13	0.06
		3	End	112.30	27.3-31.1	9.0	29.4	1.18	1.16	0.02
		4	Initial	44.50	17.0-18.4	7.7	18.6	0.97	0.99	0.64
TEST	MIDDLE	4	Intermediate	40.90	5.7-16.7	9.8	14.3	1.00	1.02	0.92
		4	End	90.90	30.2-45.2	10.8	36.6	1.12	1.11	0.24
		5	Initial	44.70	15.4-24.6	5.9	18.9	0.94	0.97	0.48
		5	Intermediate	39.90	9.4-22.9	4.3	10.1	0.99	1.00	0.8
		5	End	77.50	33.1-40.2	0.6	36.4	1.12	1.10	0.24
		3	Initial	45.10	13.9-20.0	9.9	18.1	1.02	1.03	0.76
		3	Intermediate	43.90	12.9-18.3	11.6	17.3	1.04	1.06	0.48
		3	End	98.90	24.4-33.5	6.8	29.0	1.02	1.03	0.84
		4	Initial	45.30	10.0-24.0	10.6	22.2	1.00	1.01	0.96
	END	4	Intermediate	42.00	9.2-15.8	8.5	13.6	1.04	1.06	0.56
		4	End	88.50	34.1-43.0	16.1	39.2	1.04	1.04	0.74
		5	Initial	45.90	11.4-38.5	10.0	28.6	1.04	1.03	0.76
		5	Intermediate	39.60	4.0-10.6	8.8	10.1	0.99	1.01	0.48
		5	End	83.60	22.5-45.8	16.1	39.4	1.21	1.21	0.84

Droplet Size Distribution (D50 Data) - REF Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
REF	BEG	3	Initial	53.87	33.6-78.4	14.4	59.6
		3	Intermediate	42.00	16.2-37.0	7.2	25.5
		3	End	103.60	11.9-33.2	6.1	23.4
		4	Initial	47.30	19.0-67.8	9.2	48.5
		4	Intermediate	41.10	12.1-42.0	8.2	28.5
		4	End	90.20	14.8-52.2	10.5	37.1
		5	Initial	49.30	46.3-59.6	15.6	50.3
		5	Intermediate	41.00	13.0-37.7	4.8	24.2
		5	End	74.00	19.9-42.1	9.0	40.1
	MIDDLE	3	Initial	49.20	16.3-81.1	17.9	57.7
		3	Intermediate	42.30	11.7-43.0	9.2	28.5
		3	End	95.30	21.0-28.1	6.2	23.4
		4	Initial	46.10	25.2-43.2	11.4	36.7
		4	Intermediate	40.70	15.7-38.3	5.2	26.0
		4	End	81.00	28.6-42.9	10.5	36.3
		5	Initial	47.40	24.3-46.7	6.1	37.8
		5	Intermediate	40.50	8.9-38.4	5.8	25.8
		5	End	69.30	30.6-33.8	11.6	31.3
	END	3	Initial	44.40	14.9-30.1	7.9	23.7
		3	Intermediate	42.10	13.5-36.2	9.5	25.9
		3	End	97.10	18.1-49.1	15.0	34.0
		4	Initial	45.40	19.6-40.5	10.4	30.9
		4	Intermediate	40.50	14.9-41.3	7.6	28.0
		4	End	85.30	28.7-54.7	17.8	42.6
		5	Initial	44.10	17.9-33.9	4.5	22.1
		5	Intermediate	40.00	14.3-37.0	7.4	25.1
		5	End	68.90	29.6-50.6	7.6	39.7

Droplet Size Distribution (SPAN Data) - Test Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean (N=30)	Geo Mean (N=30)	P
		3	Initial	2.49	38.6-48.7	2.1	43.2	0.80	0.91	0.06
		3	Intermediate	3.80	12.0-22.8	4.5	18.1	1.00	1.02	0.82
		3	End	1.70	18.6-21.9	4.5	20.2	0.94	0.93	0.08
		4	Initial	2.70	28.6-46.1	18.1	41.0	0.93	0.95	0.52
	BEG	4	Intermediate	3.60	8.8-31.2	11.9	21.5	0.90	0.92	0.12
		4	End	1.97	27.0-30.0	3.2	28.2	0.94	0.93	0.28
		5	Initial	2.60	41.8-51.8	11.6	46.1	0.93	0.95	0.56
		5	Intermediate	3.60	22.2-27.6	5.1	26.9	0.94	0.96	0.36
		5	End	2.40	20.3-33.1	13.9	26.9	0.93	0.94	0.32
		3	Initial	2.80	32.1-55.9	13.0	41.6	1.22	1.23	0.16
		3	Intermediate	3.70	15.4-23.4	10.2	20.9	0.93	0.95	0.22
		3	End	1.70	17.0-31.4	3.4	23.1	0.89	0.87	0.02
		4	Initial	2.70	31.8-42.9	2.2	36.8	0.93	1.00	0.68
TEST	**MIDDLE**	4	Intermediate	3.80	12.8-28.9	6.7	24.4	0.95	0.93	0.32
		4	End	2.00	20.9-24.4	5.0	22.7	0.88	0.87	0.04
		5	Initial	2.60	35.3-45.9	23.1	43.4	0.96	0.97	0.6
		5	Intermediate	3.90	20.5-26.3	2.8	24.1	1.03	1.04	0.88
		5	End	2.50	28.5-32.0	8.8	28.8	0.86	0.89	0.06
		3	Initial	2.30	40.0-49.5	9.5	42.3	0.88	0.89	0.22
		3	Intermediate	3.20	20.2-34.9	4.2	26.4	0.84	0.86	0.02
		3	End	2.00	25.5-29.6	5.5	26.7	1.00	1.02	0.96
		4	Initial	2.70	29.2-40.6	9.0	32.6	1.00	1.03	0.88
	END	4	Intermediate	3.70	9.1-33.8	4.0	23.3	1.03	1.05	0.64
		4	End	2.20	21.9-31.8	15.0	28.1	0.92	0.93	0.32
		5	Initial	2.70	35.4-47.2	14.1	40.4	1.13	1.15	0.22
		5	Intermediate	3.40	8.0-43.9	17.7	32.9	1.03	1.02	0.02
		5	End	2.30	17.9-36.0	16.5	29.8	0.88	0.87	0.96

Droplet Size Distribution (SPAN Data) - REF Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
REF	BEG	3	Initial	3.10	28.4-47.7	16.1	42.4
		3	Intermediate	3.80	26.4-31.9	9.9	30.5
		3	End	1.80	11.7-22.8	6.1	19.6
		4	Initial	2.90	32.8-51.0	21.5	44.9
		4	Intermediate	4.00	22.9-32.9	7.1	27.7
		4	End	2.10	13.4-45.9	5.6	31.5
		5	Initial	2.80	42.6-46.3	6.0	48.6
		5	Intermediate	3.80	25.6-31.9	4.1	29.3
		5	End	2.60	21.9-38.0	7.1	28.2
	MIDDLE	3	Initial	2.30	46.1-55.1	13.2	48.7
		3	Intermediate	4.00	8.1-37.5	7.3	25.9
		3	End	1.90	17.6-20.9	9.9	20.1
		4	Initial	2.90	40.6-52.5	3.5	44.1
		4	Intermediate	4.00	23.3-29.9	3.1	26.7
		4	End	2.30	28.1-32.2	7.6	30.1
		5	Initial	2.70	42.6-56.2	12.1	48.3
		5	Intermediate	3.80	23.1-30.7	4.4	32.5
		5	End	2.90	29.5-33.2	8.9	27.7
	END	3	Initial	2.60	37.0-43.5	11.9	39.1
		3	Intermediate	3.80	26.0-35.6	0.5	29.2
		3	End	2.00	14.9-39.4	14.8	30.5
		4	Initial	2.70	41.5-44.7	8.3	42.1
		4	Intermediate	3.60	23.8-39.3	7.3	31.9
		4	End	2.40	21.1-32.7	15.9	31.9
		5	Initial	2.40	42.9-58.1	11.3	51.4
		5	Intermediate	3.30	25.2-34.3	11.4	32.9
		5	End	2.60	21.9-34.2	1.7	30.3

Comments on Droplet Size Distribution

Based on droplet size distribution plots for individual sprays (percent transmission vs. time along with D10, D50, D90) submitted on 11 January 2001, the data supporting droplet size distribution by laser diffraction are unacceptable. This is because aberrant, and apparently random, spikes occur in the D50 data in the intermediate (fully formed plume) phase of the spray. These spikes represent up to approximately 3 times the magnitude of most D50 values in the same plot. These spikes were observed at all distances, and represent excessive and unacceptable variability during the most stable portion of the plume. This represents much greater variability than the DBE has observed with other data sets.

It is not clear if the aberrant spikes are a characteristic of the device or occur due to a problem with the method. For example, the spikes may occur due to reentry of large droplets into the path of the laser beam as a result of inadequate airflow. The firm will be asked if the influence of airflow rate on the variability of D50 was studied as part of method validation. After correcting the problem, the firm should provide complete droplet size distribution data using a method that eliminates the aberrant spikes. The repeat testing should be performed using the same three lots of the test and reference products, if these batches are still within the expiry date.

For each spray the firm should provide D10, D50, D90 and Span data for the following stages of plume life based on % obscurations (or transmission) of the laser beam:

A. Plume formation characterized by increase in % obscuration or decrease in % transmission.

B. Fully formed plume characterized by a period of relatively stable obscuration/transmission.

C. Dissipating plume characterized by decrease in obscuration or increase in transmission relative to B.

The revised droplet size distribution data should be accompanied by a revised SOP and representative (≥ 20%) plots of obscuration/transmission vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs.

time data. Furthermore, if possible, data regarding the duration of "fully formed plume" of test and reference products should also be submitted.

b. Cascade impaction: The cascade impactor characterizes particles in a smaller size range than the expected range for aqueous nasal sprays. However, it is useful as to assure that there is not an excess mass of "fines" in the test product relative to the RLD. Cascade impactor (————) data should account for mass balance and be reported in the following groups:

Group-1: From valve stem and actuator up to top stage (stage zero).
Group-2: One stage below the top stage.
Group-3: Everything from 2nd stage through the filter.

The firm was asked to provide cascade impactor studies only at the beginning and end of canister through-life testing.

Firm's Response

The firm submitted the following data:

Collection #	Corresponding Stages	Aerodynamic Diameter (um)
Group 1	Collar, induction Port, Inlet Cone, Stage 0, Valve stem & Actuator	>9.0
Group 2	Stage 1	<9.0
Group 3	Stage 2 to 7 and Filter	<4.7

The drug deposited on corresponding stages was determined separately by HPLC method. For the HPLC method, the LOQ was ——— ———.

Ten units from each of the 3 unit lots of test and reference products were used to obtain cascade impaction data equipped with *USP throat*. Each unit was tested at the beginning and end of life.

The procedure for determination of particle size distribution using ——————— Cascade Impactor (using Automated Spray Pump Actuation Station ———————) and HPLC method

for the assay of Butorphanol Tartrate was validated for precision, accuracy, specificity and linearity (Vol. 3.7, page 2496). A summary of cascade impaction data based on the reviewer calculation is presented in the Table IV.

Table IV

Material Recovered(%)

PROD.	SECTOR	Mean(N=30) Group 1	Variability %CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Geom Mean (N = 30)	p
				(>9.0 um)			
TEST	BEG	98.96	1.5-3.2	0.5	2.6	1.03 1.03	0.00003
	END	97.71	1.4-3.2	0.7	2.2	1.04 1.04	0.008
REF	BEG	96.07	1.4-3.4	1.1	2.4		
	END	94.40	2.1-10.5	2.4	6.5		

PROD.	SECTOR	Mean(N=30) Group 2	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Geom Mean (N = 30)	P
				(<9.0 ->4.7 um)			
TEST	BEG	0.05	44.5-59.2	28.6	77.1	0.71 XXX*	0.17
	END	0.06	23.3-40.0	10.2	35.7	0.86 XXX	0.17
REF	BEG	0.07	38.8-98.6	22.9	74.6		
	END	0.07	41.7-101.3	20.8	71.8		

PROD.	SECTOR	Mean(N=30) Group 3	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Geom Mean (N = 30)	P
				(<4.7 um)			
TEST	BEG	0.18	12.1-22.8	11.8	24.4	0.82 0.83	0.03
	END	0.21	10.6-33.5	9.5	24.5	0.84 0.89	0.15
REF	BEG	0.22	16.6-50.2	18.2	39.88		

END	0.25	23.5-89.0	8.2	57.0

* Geometric means are not estimable.

Comment on Cascade Impaction Data:

1. The Cascade Impaction results indicated that the amount of drug deposed in droplets >9 um is similar between test and reference products. Therefore, there is not an excess mass of fines in the test product relative to the reference product.

2. The amount of drug collected in groups 2 and 3 constitute <0.4% of the total drug collected from the cascade impactor apparatus. This fraction represents' fine particles (<9.0 um in diameter). Based on the test/ref ratio, the test product contains fewer fine particles. The reviewer considers that the amount deposited in groups 2 and 3 is negligible compared with the quantity of drug received in group 1. Therefore, the test and reference equivalence is based on group 1 data. Based on that data, the test/ref ratios were within the limits of 90-111% stipulated in the draft Nasal BA/BE Guidance.

3. The firm's response to the comment is acceptable.

DBE Comment III:

Spray Pattern

Spray patterns should be determined at three distances from the TLC plate at beginning and end life sectors. Spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug-specific reagent. A drug-specific reagent will not develop color when tested with placebo. Photographs of spray patterns, in color if appropriate, should be analyzed to measure the shortest (D_{min}) and widest (D_{max}) diameters. The firm was asked to report values of D_{min}, D_{max} and ovality ratio (D_{max}/D_{min}), along with photographs and markings indicating D_{min} and D_{max}.

Firm's Response:

The firm submitted spray pattern data at three distances (5, 4 and 2.5 cm) from TLC plate at beginning and end life sectors for the test product and the reference product. It provided individual results of spray pattern determination in term of D_{max}, D_{min} and ovality ratio (D_{max}/D_{min}).

The firm provided color photocopies of corresponding TLC plates with markings indicating D_{max} and D_{min} (Attachment No. 4B, Vol.1.8). The staining agent (————————————) that reacts with drug was used to highlight the pattern of the TLC plate. No pattern was detected with a placebo spray. Test Method No. TM-1183 (Spray Pattern Determination for Butorphanol Tartrate Nasal Spray 10 mg/mL) can be found in Attachment No. 4C (Vol. 3.8), along with its corresponding validation report.

A summary of the spray pattern data based on the reviewer's calculations is presented in Table V.

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Table V

Spary Pattern Data - Test Product

PROD.	Sector	Distance	Parameter	Mean	Variability (%CV) Within-Lot	Between-lot	Total	TEST/REF (N=30)		p
				(N = 30)	(N=10)	(N=3)	(N=30)	Airth. Mean	Geo. Mean	
		2.5	Long. Diam.	3.50	6.6-8.1	1.6	7.3	0.90	0.90	0.001
		2.5	Short. Diam.	3.20	6.4-9.4	4.8	8.4	0.95	0.95	0.04
		2.5	Oval. Ratio	1.10	3.9-4.1	2.3	4.2	0.94	0.94	0.03
		4	Long. Diam.	4.90	6.7-9.4	4.2	8.0	0.91	0.92	0.01
	BEG	4	Short. Diam.	4.30	8.2-9.7	6.2	10.0	0.99	0.99	0.36
		4	Oval. Ratio	1.10	4.6-7.4	2.2	6.1	0.92	0.92	0.01
		5	Long. Diam.	5.90	7.4-10.3	0.0	8.5	0.92	0.92	0.01
		5	Short. Diam.	5.00	6.9-9.6	5.7	9.2	1.00	1.00	0.44
TEST		5	Oval. Ratio	1.20	6.5-7.0	5.4	8.1	0.91	0.92	0.01
		2.5	Long. Diam.	3.53	6.0-6.9	1.7	6.3	0.89	0.90	0.0004
		2.5	Short. Diam.	3.10	5.2-7.4	4.8	7.1	0.91	0.91	0.0018
		2.5	Oval. Ratio	1.10	4.0-5.1	3.2	5.0	0.97	0.97	0.036
		4	Long. Diam.	4.80	5.9-10.0	4.3	8.1	0.88	0.88	0.0014
	END	4	Short. Diam.	4.20	7.4-9.0	7.7	10.2	0.92	0.93	0.0087
		4	Oval. Ratio	1.10	5.5-9.4	4.2	7.6	0.96	0.95	0.0536
		5	Long. Diam.	5.70	6.0-7.8	2.6	7.0	0.90	0.92	0.003
		5	Short. Diam.	4.80	7.7-11.2	8.4	11.4	0.96	0.97	0.135
		5	Oval. Ratio	1.20	5.6-8.0	5.0	8.2	0.94	0.94	0.0583

Spray Pattern Data - REF Product

PROD.	Sector	Distance	Pume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
		2.5	Dmax	3.93	6.5-16.5	11.4	14.9
		2.5	Dmin	3.40	6.8-13.2	6.2	12.3
		2.5	Oval. Ratio	1.20	3.3-24.9	7.3	17.3
		4	Dmax	5.40	5.3-17.2	14.2	16.3
	BEG	4	Dmin	4.40	9.4-15.9	7.0	14.1
		4	Oval. Ratio	1.20	5.9-26.1	8.3	18.9
		5	Dmax	6.40	9.2-18.0	11.8	15.7
		5	Dmin	5.00	11.3-16.1	6.4	14.5
REF		5	Oval. Ratio	1.30	9.3-28.7	7.0	20.7
		2.5	Dmax	3.95	6.0-15.9	12.7	15.6
		2.5	Dmin	3.50	6.0-12.1	9.4	12.5
		2.5	Oval. Ratio	1.10	3.2-8.6	4.0	7.5
		4	Dmax	5.50	6.5-19.0	13.1	16.9
	END	4	Dmin	4.50	6.9-14.7	7.1	11.6
		4	Oval. Ratio	1.20	5.3-17.5	6.6	13.5
		5	Dmax	6.40	7.0-18.4	10.5	15.7
		5	Dmin	5.00	10.4-13.6	6.0	12.9
		5	Oval. Ratio	1.30	7.7-26.0	6.4	19.2

Comments on Spray Pattern Analysis:

1. The total variability (%CV) for the test product is less than for the reference product for the various distances and stages (beginning and end life sectors).

2. The ratios of the test geometric means to the reference geometric means for D_{min} and Ovality were within 0.91-1.0 and 0.92-0.97 range, respectively. Test/ref ratios of geometric means are within the 90-111% range stipulated in the draft Nasal BA/BE Guidance.

3. For the D_{max}, the test/ref ratios based on geometric means were 0.88-0.92. It is noted that the mean performance of the test and reference products did not change from beginning to end of product use. Therefore, D_{max} data for these stages were combined. Based on the combined data the test/ref ratio was within the 90-111% range stipulated in the draft Nasal BA/BE Guidance.

4. Based on the mean data, values of D_{max} and D_{min} did not significantly change between the beginning and end life sectors. The total variability of the test product was less than that of the reference product.

5. The test product's total variability was less than that of the reference product.

6. The spray pattern data are acceptable.

DBE Comment IV:

Plume Geometry

Plume geometry describes two side views, at a 90^0 angle to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. The firm was asked to provide plume geometry based on high speed photography. Plume geometry may be performed only at beginning of use life. Plumes should be characterized at three or more delay times after actuation. These times should be chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time. Photographs of spray plumes should be used to measure plume length, plume width, and plume (spray cone) angle. The firm was asked to provide all photographs and data characterizing plume dimensions including scaling information to indicate actual size.

Firm's Response:

The plume geometry test was performed by [redacted] on behalf of Novex Pharma.

The test consisted of using 10 units from each product lot to obtain plume geometry measurements at three time delays (0.002, 0.105 and 0.208 seconds).

The plume length and width measurements were taken using spray Nos. 5, 6 and 7 at a 0^{o} angle and spray Nos. 8, 9 and 10 at a 90^{o} angle. The spray plumes were characterized at the above three delay times, representing the beginning, middle and end of plume formation. The results of the plume length and width measurements are shown in Attachment No. 5A (Vol. 3.1). Photographs of the spray plumes used to measure the plume length and width are shown in Attachment No. 5B (Vol. 3.1 and 3.2).

The plume angle measurements were taken using spray Nos. 11, 12 and 13 at a 0^{o} angle and spray Nos. 14, 15 and 16 at a 90^{o} angle. The results of the spray angle measurements are shown in Attachment No. 5C (Vol. 3.2). Photographs of the spray plums used to measure the plume angle are shown in Attachment No. 5D (Vol. 3.2 and 3.3). The firm indicated that no angle measurements of aerosol plumes were possible after the period of plume formation (initial image at 0.002 seconds post actuation). The plume geometry results calculated by the reviewer are shown in Table VI, all data presented are the means of 3 sprays.

Table VI

Plume Geometry Data (Plume Length)

PROD.	Delay (sec)	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith (N = 30)	Geo (N = 30)	p
			0-Degree View					
	0.002	10.15	7.6-14.0	13.1	15.5	1.13	1.15	0.02
TEST	0.105	32.93	7.7-13.9	2.9	10.3	1.10	1.10	0.004
	0.208	46.34	3.4-9.3	2.4	6.3	1.10	1.10	0.002
	0.002	9.01	19.7-30.6	14.0	28.1			
REF	0.105	29.97	6.3-13.9	3.8	10.5			
	0.208	42.11	5.8-12.2	4.2	9.8			
			90-Degree View					
	0.002	11.89	7.7-14.3	12.4	15.2	1.13	1.14	0.001
TEST	0.105	33.45	7.1-14.5	2.5	10.1	1.08	1.09	0.004
	0.208	46.93	4.2-7.6	4.2	6.9	1.09	1.09	0.01
	0.002	10.48	14.6-23.5	10.0	20.9			
REF	0.105	30.88	8.0-13.7	5.9	11.7			
	0.208	43.16	6.3-13.4	5.3	10.8			

Plume Geometry Data (Plume Width)

PROD.	Delay (sec)	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith (N = 30)	Geo (N = 30)	P
			0-Degree View					
	0.002	5.05	13.3-20.5	14.9	20.8	0.95	0.97	0.34
TEST	0.105	19.88	9.5-12.6	4.8	11.3	1.02	1.03	0.74
	0.208	21.21	10.4-11.6	4.3	11.3	1.00	1.00	0.92
	0.002	5.31	18.3-24.8	23.6	29.2			
REF	0.105	19.45	8.7-15.9	8.8	14.7			
	0.208	21.28	6.5-12.2	9.8	12.6			
			90-Degree View					
	0.002	5.62	11.5-21.6	18.1	22.7	0.90	0.91	0.02
TEST	0.105	19.61	7.8-9.2	4.2	8.8	1.00	1.00	0.66
	0.208	20.64	5.3-11.1	5.0	9.0	0.95	0.96	0.36
	0.002	6.24	18.9-26.6	20.7	28.3			
REF	0.105	19.77	8.2-21.9	8.3	16.5			
	0.208	21.70	8.4-19.2	6.8	14.1			

Plume Geometry Data (Plume Angle)

PROD.	Delay (sec)	Mean (N = 10)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith (N = 30)	Geo (N = 30)	P
			0-Degree View					
TEST	0.002	43.10	10.1-19.0	7.9	15.3	0.89	0.89	0.04
REF	0.002	48.57	17.0-21.1	14.6	22.4			
			90-Degree View					
TEST	0.002	41.63	11.7-15.6	9.8	15.2	0.87	0.87	0.02
REF	0.002	48.07	15.6-23.1	15.0	23.1			

Comments on Plume Geometry Data:

1. The test/reference ratios for plume length ranged from 1.10 to 1.15 at 0^{o} angle and from 1.09 to 1.14 at 90^{o} angle. For plume length the differences between test and reference products were statistically significant at the three delay times. The middle delay time (105 msec) represents fully formed plume. At that delay time test/ref ratios were in the range of 1.09-1.10.

2. For plume width test/reference ratios ranged from 0.97 to 1.03 at 0^{o} angle and from 0.91 to 1.00 at 90^{o} angle. For plume width the differences between test and reference products were statistically insignificant at the three delay times except at 0.002 sec at 90^{o} angle. Test/ref ratios at the middle delay time were in the range of 1.00-1.03.

3. Of the three delay times, 105 and 208 msec may represent the fully formed and dissipating plumes, respectively. At these delay times the ratio of means for plume length and width were in the range of 1.09-1.10 and 0.96-1.03, respectively and they are within the 90-111% range stipulated in the draft Nasal BA/BE Guidance. The plume length and plume width data are acceptable.

4. Based one individual delay time (0.002 sec) the test/reference ratios for plume angle were 0.89 at 0^{o}

angle and 0.87 at 90° angle. For plume angle the differences between test and reference products were statistically significant. It should be noted that the plume angles were measured at a delay time of 2 msec which represents the very initial phase of plume formation rather than the fully formed plume. The firm did not report plume angle at later times. Plume angle data submitted by the firm do not represent the angle of the fully formed plume. Therefore, the plume geometry data are incomplete.

5. For all three parameters (plume length, plume width and plume angle) total variability of the test product was less than that of the reference product.

III. Overall Comments:

1. The composition of the test product is qualitatively and quantitatively the same as the reference product.

2. Based on the test/reference ratios the unit dose data indicate that the test and reference products are similar at the beginning and end of unit life. The overall variability for the test and reference products is very low.

3. The tail-off characteristics of the test product are similar to those of the reference product.

4. The droplet size distribution data are unacceptable due to comments given above.

5. The spray patterns produced by the test and reference products were evaluated for comparative shape (based on ovality ratio) and size (based on D_{min} and D_{max}). The test and reference products produced similar spray patterns.

6. Plume geometry was characterized by plume angle, plume height, and plume width. The plume geometry data are incomplete due to a deficiency in the plume angle data.

7. On June 29, 2000 the firm submitted an amendment proposing the use of a new metering nasal pump. ——— ——— manufactures the new pump (referred to as "Pump B", which is the same company that manufactured the original pump ("Pump A"). With respect to functionality, the firm indicated that ——— has confirmed that Pumps A

and B are identical, as supported by the fact that the two pumps have the same schematic drawing. A copy of this drawing is attached. A comparison of the physical dimensions between Pumps A and B is attached. The firm also indicated that the only differences between Pumps A and B are in the material of construction in certain parts (———) of the pumps. The firm stated that these differences in Pump B are advantageous from a quality control perspective. A comparison of materials of construction for Pump A and Pump B using differential scanning calorimeter or IR is attached.

In order to demonstrate the functional equivalence of Pump A and B, Novex submitted results of limited *in vitro* testing including dose uniformity, spray pattern, droplet size distribution by laser diffraction and particle size distribution by Cascade Impaction. The results of these testings are attached. From the data submitted, Pumps A and B are similar with regard to drug delivery (*in vitro* performance). Therefore, the firm proposal for using Pump B is granted.

8. Methods for statistical analysis of *in vitro* performance data given in the draft NASAL BA/BE guidance are still under development. Therefore, those methods are not implemented at this time. The evaluation of the *in vitro* equivalence of test and reference product is based on ratio of geometric means and consideration of relative variability (%CV) of test and reference products. Based on the relevant ratio of means, the test product performance with regard to unit dose, priming/repriming, cascade impaction and spray pattern was within the limit of 90-111%, stipulated in the draft Nasal BA/BE Guidance.

IV. Recommendation:

The *in vitro* performance testing conducted by Novex Pharma on its Butorphanol Tartrate Nasal Spray, 10 mg/mL comparing it with the reference product, Stadol®, nasal solution (Bristol-Myers) has been found incmoplete due comments 4 and 6.

Moheb H. Makary

Moheb H. Makary, Ph.D. Date: 4/16/01
Review Branch III
Division of Bioequivalence

bmd 3/28/01
4/13/01

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Barbara M Davit Date: 4/16/01

Concur: Dale P. Conner Date: 4/20/01
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HFD-658/ Bio team Leader B. Davit

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MHM
HFD-658/ Bio team Leader B. Davit BMD 4/16/01
HFD-655/ Bio GJP Singh CODS
HFD-650/ D. Conner APK 4/20/01

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Printed in final on 4/6/01

BIOEQUIVALENCY - DEFICIENCIES Submission Date:8-22-00

1.	**STUDY AMENDMENT** (STA) 8/22/00	Strengths: 10 mg/mL **Outcome: IC**
2.	**STUDY AMENDMENT** (STA) 6/29/00	Strengths: 10 mg/mL **Outcome: IC**
3.	new correspondence (NC) 31 **STUDY AMENDMENT** ~~(STA)~~ 10/~~30~~/00	Strengths: 10 mg/mL **Outcome: IC**
4.	15 **STUDY AMENDMENT** (STA) 1/~~11~~/01	Strengths: 10 mg/mL **Outcome: IC**

Outcome Decisions: IC - Incomplete

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-499 APPLICANT: Novex Pharma

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Based on the droplet size distribution plots for individual sprays (percent transmission vs. time along with D10, D50, D90) submitted on 11 January 2001, the data supporting droplet size distribution by laser diffraction are unacceptable. This is because aberrant, and apparently random, spikes occur in the D50 data in the intermediate (fully formed plume) phase of the spray. These spikes represent up to approximately 3 times the magnitude of most D50 values in the same plot. These spikes were observed at all distances, and represent excessive and unacceptable variability during the most stable portion of the plume. This is much greater variability than has been observed in laser diffraction analyses, hitherto.

The variability may be due to your performance of the method or may be a characteristic of your product. Please investigate your method to determine if it is being applied appropriately. For example, the aberrant spikes may occur due to reentry of large droplets into the path of the laser beam as a result of inadequate airflow. The influence of airflow rate on the variability of D50 should be investigated during method validation. After correcting the problem, please provide complete droplet size distribution data. The repeat test should be performed using the same three lots of the test and reference products, if these batches are still within the expiry date.

For each spray, please provide D10, D50, D90 and Span data for the following stages of plume life based on % obscurations (or transmission) of the laser beam:

A. Plume formation characterized by increase in % obscuration or decrease in % transmission.

B. Fully formed plume characterized by a period of relatively stable obscuration/transmission.

C. Dissipating plume characterized by decrease in obscuration or increase in transmission relative to B.

Please provide a revised SOP and representative (≥ 20%) plots of obscuration/transmission vs. time (msec) with the revised droplet size distribution data. These graphs should also contain plots of D10, D50 and D90 vs. time data. Please also submit, if possible, data regarding the duration of "fully formed plume" of test and reference products.

2. The plume angles were measured at a delay time of 2 msec which represents the very initial phase of plume formation rather than the fully formed plume. Plume angle at later times was not reported. Therefore, plume angle data you submitted does not represent angle of the fully formed plume. Please provide plume angle data at later delay times. The plume angle data should include one angle measurement during plume formation when the plume is still in contact with actuator (e.g., at time delays of 10-50 msec).

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Butorphanol Tartrate
Nasal Spray, 10 mg/mL
ANDA #75-499
Reviewer: Moheb H. Makary
W 75499STA.N01

Novex Pharma
Richmond Hill, Ontario
Submission Dates:
November ~~27~~ 29, 2001

Review of an Amendment

I. Objective:

The firm has submitted its response to comments made by the Division of Bioequivalence (DBE) in its letter of April 30, 2001).

II. Review of the Amendment:

Drug Products:

Test: The firm's original ANDA exhibit batch (lot #8X190) has expired; therefore, the firm manufactured an additional batch of Butorphanol Tartrate Nasal Spray (lot #1X260) in order to perform the analyses requested below. Novex Pharma's Butorphanol Nasal Spray, 10 mg/mL, consisted of one lot of the drug solution formulation (Lot #1X260), Lot size ———, divided into three sublots using three separate batches of pumps (Novex Pharma QC Nos. 5325, 4406 and 5806). Lot #5284 of the nasal spray pumps used in the previous studies has been depleted and was replaced by a new lot #5806.

Reference: Bristol-Myers Squibb's Stadol NS^{R}, 10 mg/mL; Lots 0H29692 Exp. 8/2002, 0J30529 Exp. 9/2002 and 0L31505 Exp. 11/2002. All three lots used in original submission had expired or stock has been depleted. Therefore, the firm has purchased the three new lots of the RLD mentioned above in order to perform the required testing.

DBE Comment #I

Droplet size distribution

> *1. Based on the droplet size distribution plots for individual sprays (percent transmission vs. time along with D10, D50, D90) submitted on 11 January 2001, the data supporting droplet size distribution by laser diffraction are unacceptable. This is because aberrant, and apparently random, spikes occur in the*

D50 data in the intermediate (fully formed plume) phase of the spray. These spikes represent up to approximately 3 times the magnitude of most D50 values in the same plot. These spikes were observed at all distances, and represent excessive and unacceptable variability during the most stable portion of the plume. This is much greater variability than has been observed in laser diffraction analyses, hitherto.

The variability may be due to the performance of the method or may be a characteristic of the product. The was asked to investigate the method to determine if it is being applied appropriately. For example, the aberrant spikes may occur due to reentry of large droplets into the path of the laser beam as a result of inadequate airflow. The influence of airflow rate on the variability of D50 should be investigated during method validation. After correcting the problem, the firm was asked to provide complete droplet size distribution data. The repeat test should be performed using the same three lots of the test and reference products, if these batches are still within the expiry date.

For each spray, the firm was asked to provide D10, D50, D90 and Span data for the following stages of plume life based on % obscurations (or transmission) of the laser beam:

A. *Plume formation characterized by increase in % obscuration or decrease in % transmission.*

B. *Fully formed plume characterized by a period of relatively stable obscuration/transmission.*

C. *Dissipating plume characterized by decrease in obscuration or increase in transmission relative to B.*

The firm was asked to provide a revised SOP and representative (≥ 20%) plots of bscuration/transmission vs. time (msec) with the revised droplet size distribution data. These graphs should also contain plots of D10, D50 and D90 vs. time data. The firm was asked to submit, if possible, data regarding the

duration of "fully formed plume" of test and reference products.

Firm's Response

The firm indicated that the original droplet size distribution data were collected using equipment located in an enclosed area and, although provisions were made for adequate airflow, the repetition of the sprays did have an effect on the data, hence the noted aberrant spikes in the spray profiles. After a vacuum system was installed above the spray path to prevent droplets from re-entering the path of the laser beam, the aberrant spikes were not observed in the repeated droplet size distribution studies. The representative plots (20%) of transmission (%) vs. time (msec), including D10, D50 and D90 vs. time data, are provided in Attachment No. 7, Vol. 7.1.

Droplet size determination was performed on 10 units from each of the 3 unit lots of test and reference products. Each unit was tested at beginning, middle, and end sectors of unit life. At each sector of unit life, each unit was actuated at three distances (3 cm, 5 cm, and 8 cm) relative to the [redacted] laser beam.

Bioequivalence evaluation is based on D50 and SPAN data. A summary of these data based on the reviewer's calculations is given in Table I.

Table I
Droplet Size Distribution (D50 Data) - Test Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo	p
TEST	BEG	3	Initial	44.44	10.1-12.7	8.99	13.71	0.88	0.88	0.003
		3	Intermediate	35.56	8.2-10.7	9.70	12.34	0.90	0.90	0.003
		3	End	93.91	5.5-26.0	16.22	21.85	1.06	1.06	0.250
		5	Initial	41.61	7.8-13.1	5.69	10.95	0.90	0.90	0.009
		5	Intermediate	34.86	5.1-6.1	4.17	6.33	0.92	0.93	0.009
		5	End	60.47	13.1-25.4	15.08	24.40	1.01	1.01	0.894
		8	Initial	47.38	5.2-9.2	2.87	8.06	0.94	0.94	0.006
		8	Intermediate	39.74	4.5-4.9	1.87	4.82	0.95	0.95	0.002
		8	End	45.77	4.9-10.4	3.58	7.57	0.98	0.98	0.285
	MIDDLE	3	Initial	43.34	11.7-16.1	8.12	14.84	0.77	0.77	0.000
		3	Intermediate	35.55	10.3-12.7	9.52	13.50	**0.80**	**0.80**	0.000
		3	End	82.84	13.5-23.5	7.81	20.79	0.91	0.91	0.161
		5	Initial	44.27	6.9-20.2	9.04	15.84	0.84	0.84	000
		5	Intermediate	35.30	5.3-8.2	5.13	7.82	**0.85**	**0.86**	000
		5	End	51.66	9.0-21.3	9.22	18.51	0.83	0.83	0.001
		8	Initial	49.72	6.7-9.4	5.09	9.25	0.87	0.87	000
		8	Intermediate	40.80	3.4-8.6	3.93	7.15	**0.89**	**0.89**	000
		8	End	43.98	4.2-16.7	3.32	10.89	0.94	0.94	0.029
	END	3	Initial	48.30	13.5-15.1	9.38	15.94	0.92	0.92	0.045
		3	Intermediate	37.27	11.7-13.5	10.13	14.75	0.91	0.91	0.029
		3	End	76.06	13.7-29.7	10.51	23.53	1.04	1.04	0.484
		5	Initial	46.16	9.2-11.8	3.33	10.80	0.94	0.94	0.063
		5	Intermediate	36.81	4.7-11.1	3.36	8.86	0.96	0.96	0.124
		5	End	51.83	11.5-33.7	7.92	27.10	1.02	1.02	0.737
		8	Initial	50.71	5.1-9.8	3.15	8.35	0.96	0.97	0.137
		8	Intermediate	41.80	2.9-8.1	1.77	6.21	0.97	0.97	0.132
		8	End	43.23	4.7-10.0	2.08	7.02	0.97	0.97	0.063

Droplet Size Distribution (D50 Data) - REF Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
REF	BEG	3	Initial	50.60	6.7-17.5	10.24	15.77
		3	Intermediate	39.71	9.6-18.6	10.18	17.91
		3	End	88.80	13.5-27.7	8.25	22.75
		5	Initial	46.08	5.0-18.6	6.25	15.04
		5	Intermediate	37.86	7.7-19.8	5.33	14.36
		5	End	60.03	21.2-25.4	13.56	25.54
		8	Initial	50.40	6.2-11.9	3.73	9.11
		8	Intermediate	41.67	4.2-9.3	2.72	7.41
		8	End	46.79	5.0-11.6	2.11	8.88
	MIDDLE	3	Initial	56.31	11.1-22.3	4.43	17.51
		3	Intermediate	44.63	12.1-19.6	6.71	17.44
		3	End	90.56	21.7-26.0	0.21	22.72
		5	Initial	52.62	9.9-21.6	0.67	16.07
		5	Intermediate	41.41	8.8-16.4	2.36	13.73
		5	End	62.42	22.5-23.0	7.99	22.98
		8	Initial	57.04	7.5-17.4	0.42	12.79
		8	Intermediate	45.83	6.0-16.4	1.09	11.22
		8	End	46.95	8.0-12.4	3.14	10.30
	END	3	Initial	52.63	8.6-18.4	11.04	15.85
		3	Intermediate	40.79	9.1-15.5	12.00	15.72
		3	End	73.39	14.3-24.8	11.24	21.42
		5	Initial	49.16	8.1-14.5	5.04	12.10
		5	Intermediate	38.38	6.6-11.1	5.51	10.38
		5	End	50.63	14.3-27.5	8.83	22.25
		8	Initial	52.60	8.2-10.8	2.75	9.12
		8	Intermediate	42.94	6.1-7.3	2.87	6.86
		8	End	44.68	5.4-6.3	3.53	6.33

Droplet Size Distribution (SPAN Data) - Test Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo	p
TEST	BEG	3	Initial	1.94	10.9-15.2	6.66	14.04	1.02	1.02	0.48
		3	Intermediate	2.06	3.4-12.2	4.88	9.92	0.96	0.96	0.18
		3	End	1.96	4.9-23.0	15.96	22.45	0.96	0.96	0.44
		5	Initial	1.71	5.7-9.2	4.33	8.60	0.96	0.97	0.123
		5	Intermediate	1.74	4.1-10.6	6.12	8.40	0.91	0.91	000
		5	End	2.84	12.6-20.5	10.32	18.67	0.75	0.96	0.397
		8	Initial	1.42	3.1-14.5	6.41	10.87	0.95	0.95	0.076
		8	Intermediate	1.31	2.1-7.0	3.09	5.91	0.91	0.92	0.003
		8	End	2.99	4.1-18.8	8.29	12.97	1.02	1.03	0.551
	MIDDLE	3	Initial	1.87	6.5-13.9	4.16	10.53	1.06	1.06	0.028
		3	Intermediate	1.99	6.7-8.6	0.50	7.54	1.00	1.00	0.674
		3	End	2.19	8.2-24.0	8.31	19.63	1.11	1.11	0.061
		5	Initial	1.69	6.1-16.2	2.24	10.41	0.98	0.98	0.52
		5	Intermediate	1.72	5.4-10.7	6.62	9.82	0.91	0.91	000
		5	End	3.23	8.7-15.5	3.39	12.82	1.19	1.20	000
		8	Initial	1.36	6.5-16.9	5.15	11.94	0.96	0.96	0.156
		8	Intermediate	1.32	4.6-9.9	5.17	8.22	0.90	0.91	0.001
		8	End	2.72	18.9-22.4	7.56	21.24	1.04	1.02	0.50
	END	3	Initial	1.84	6.0-20.1	7.61	14.89	1.03	1.02	0.326
		3	Intermediate	2.03	7.8-10.4	2.15	9.44	1.00	1.00	0.70
		3	End	2.39	10.7-24.2	12.18	21.48	1.03	1.03	0.53
		5	Initial	1.69	6.9-8.0	1.37	7.08	0.98	0.98	0.31
		5	Intermediate	1.71	5.9-13.6	6.84	10.60	0.93	0.93	0.016
		5	End	3.1	14.4-18.3	2.25	16.00	1.02	1.01	0.66
		8	Initial	1.35	5.2-7.7	3.49	7.14	0.96	0.96	0.046
		8	Intermediate	1.32	4.9-9.9	6.77	9.22	0.97	0.97	0.062
		8	End	2.64	18.3-25.4	13.64	24.75	1.01	1.01	0.86

Droplet Size Distribution (SPAN Data) - REF Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
REF	BEG	3	Initial	1.89	9.0-9.6	5.34	9.90
		3	Intermediate	2.15	8.9-9.4	5.81	10.12
		3	End	2.03	12.2-27.9	9.6	22.98
		5	Initial	1.77	9.3-11.9	4.48	10.94
		5	Intermediate	1.92	10.4-12.8	7.10	12.83
		5	End	3.79	12.0-174.5	49.99	158.8
		8	Initial	1.50	7.8-15.6	5.33	12.59
		8	Intermediate	1.44	9.3-17.5	8.42	16.02
		8	End	2.93	8.3-19.4	6.45	15.25
	MIDDLE	3	Initial	1.76	7.5-14.9	4.27	11.22
		3	Intermediate	1.97	4.8-10.1	3.45	8.53
		3	End	1.97	16.1-23.0	3.44	20.18
		5	Initial	1.72	8.8-13.8	4.28	11.43
		5	Intermediate	1.88	4.9-14.3	4.58	10.83
		5	End	2.71	15.1-19.0	4.04	17.41
		8	Initial	1.42	6.4-10.3	4.60	9.44
		8	Intermediate	1.46	8.1-16.0	7.68	14.04
		8	End	2.62	13.1-17.0	2.50	14.75
	END	3	Initial	1.79	6.50-14.6	5.20	11.70
		3	Intermediate	2.01	7.0-9.6	3.31	8.43
		3	End	2.32	12.5-22.29	9.3	18.45
		5	Initial	1.73	9.8-13.0	1.73	11.60
		5	Intermediate	1.83	8.5-13.4	5.51	12.50
		5	End	3.07	9.2-16.6	7.62	14.75
		8	Initial	1.41	5.5-12.4	4.55	10.47
		8	Intermediate	1.37	5.7-10.3	5.97	9.37
		8	End	2.61	16.2-26.7	2.55	22.08

Comments on Droplet Size Distribution

1. The representative plots (20%) of % transmission vs. time (msec), including D10, D50 and D90 vs. time data, provided by the firm did not exhibit the aberrant spikes observed in the original submission.

2. Evaluation of equivalence of D50 and SPAN data is based on the intermediate portion of the test and reference product sprays, as it represents the stable portion of the plume. For the middle sector of the product life, the test/reference geometric mean ratios for D50 are outside the 0.90-1.11 range, used by the Division of Bioequivalence for acceptance of D50 data for nasal spray products. For the middle sector, the test failed to meet the 0.9-1.11 range at all three distances (3, 5 and 8 cm). Therefore, test product D50 is not bioequivalent to the reference product D50.

3. At the Agency's request, the firm also submitted plume duration data of the "fully formed plume" of test and reference products based on the laser diffraction analysis. A summary of the reviewer's analysis is presented in Table II.

Table II: Duration of the intermediate portion and the entire spray in the laser diffraction analysis

Product	Dis-tance	Spray Portion	Sector											
			Beginning				Middle				End			
			Mean	%CV	T/R	*p-val*	Mean	%CV	T/R	*p-val*	Mean	%CV	T/R	*p-val*
TEST	3 cm	Intermed.	57.6	19.4	0.89	0.0020	64.3	20.7	**0.80**	**0.0000**	69.5	17.6	0.90	0.0099
		Entire	105.1	20.5	0.95	0.2931	103.9	17.8	0.85	0.0009	104.9	13.6	0.92	0.0281
	5 cm	Intermed.	57.9	16.1	0.89	0.0036	66.0	17.3	**0.83**	**0.0003**	69.3	18.9	0.91	0.0398
		Entire	110.1	17.5	0.95	0.3376	115.3	18.4	0.89	0.0091	121.5	20.1	0.98	0.6481
	8 cm	Intermed.	53.6	21.3	0.90	0.0344	61.5	16.8	**0.79**	**0.0000**	65.9	20.4	0.92	0.0757
		Entire	132.0	15.5	0.95	0.1896	136.1	20.8	0.91	0.0518	147.1	22.2	1.01	0.9193
REF	3 cm	Intermed.	64.9	15.7			80.5	20.9			77.5	14.8		
		Entire	110.7	17.2			121.6	19.3			113.5	14.4		
	5 cm	Intermed.	64.9	17.9			79.5	22.0			75.9	15.7		
		Entire	115.3	16.9			130.3	17.8			124.4	17.7		
	8 cm	Intermed.	59.9	17.2			77.7	21.5			71.7	16.0		
		Entire	139.6	12.9			149.6	17.0			146.3	18.9		

4. Based on the above data the duration of the intermediate portion of the test product plume is different from that of the reference product. At the beginning and end sectors, the test product's spray duration is within 89-95% of that the reference product, and for most comparisons the observed differences are insignificant ($p > 0.05$). On the other hand, for the middle sector, the duration of intermediate portion of the test product plume is 17-21% shorter than that of the reference product.

Furthermore, the observed differences at the middle sector are highly significant. These data indicate that, at the middle sector, the intermediate portions of the spray plumes of the test and reference products were maintained for significantly different durations. The reviewer is uncertain regarding the impact of the observed difference in duration of the intermediate spray portion upon D50 values; it may be a contributing factor influencing the observed difference in the test and reference product values at the middle sector.

5. The ratios of the test geometric means to the reference geometric means for SPAN at initial (onset) and end of plume formation are within the acceptable 0.90-1.11 range. At middle of plume formation the ratio was between 0.90 to 1.11 with exception one value, 1.20 at 5 cm distance. For most of the comparisons the P values were not significant.

DBE Comment #II

Plume Geometry

> *The plume angles were measured at a delay time of 2 msec which represents the very initial phase of plume formation rather than the fully formed plume. Plume angle at later times was not reported. Therefore, plume angle data the firm submitted does not represent angle of the fully formed plume. The firm was asked to provide plume angle data at later delay times. The plume angle data should include one angle measurement during plume formation when the plume is still in contact with actuator (e.g., at time delays of 10-50 msec).*

Firm's Response

The indicated that the original plume geometry analyses were performed by the contract testing laboratory, [redacted]. However, due to limitations with [redacted]'s equipment, they are not able to provide the requested data. The firm employed the [redacted] equipment to conduct the above-requesting test.

The firm provided plume angle data from a single frame, rather than cumulative data from numerous frames from each stage of the plume. The delay time of the single frame representing the fully formed plume was approximately 35 msec.

A summary of these data based on the reviewer's calculations is given in Table II.

Table II

Plume Geometry Data (Plume Angle)

PROD.	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith (N = 30)	Geo	P
		0-Degree View					
TEST	75.04	3.0-4.8	2.81	4.6	1.02	1.02	0.074
REF	73.52	2.8-4.1	1.43	3.67			
		90-Degree View					
TEST	75.50	3.5-4.7	3.25	4.71	1.02	1.02	0.033
REF	73.80	2.6-5.2	1.69	3.92			

Comments on Plume Geometry Data:

1. The test/reference ratios for plume angle were 1.02 at 0° angle and 90° angle. The variability of the test and reference products was comparable.

2. The firm has previously submitted acceptable data for the plume length and plume width for its test product.

3. Based on all three parameters, plume geometry data are acceptable.

III. Recommendation:

The *in vitro* performance testing conducted by Novex Pharma on its Butorphanol Tartrate Nasal Spray, 10 mg/mL comparing it with the reference product, Stadol®, nasal solution (Bristol-Myers) has been found incomplete due to comment #2 in the droplet size distribution section.

Moheb H. Makary

Moheb H. Makary, Ph.D. Date: 1/17/02
Review Branch III
Division of Bioequivalence

BDW 1/16/02
1/17/02

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Date: 2/22/02

Concur: Date: 2/27/2002
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/1-14-2002, 1-17-02
cc: ANDA #75-499, original, HFD-658 (Makary), Drug File, Division File.

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-499 APPLICANT: Novex Pharma

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Evaluation of equivalence of D50 and SPAN data is based on the intermediate portion of the test and reference product sprays, as it represents the stable portion of the plume. For the middle sector of the product life, the test/reference geometric mean ratios for D50 are outside the 0.90-1.11 range, used by the Division of Bioequivalence for acceptance of D50 data for nasal spray products. For the middle sector, the test failed to meet the 0.9-1.11 range at all three distances (3, 5 and 8 cm). Therefore, the test product D50 is not equivalent to the reference product D50.

In response to the Agency's request, you submitted the spray plume duration data. Though such data are not evaluated to determine product equivalence, your data were analyzed to determine similarity in spray plume duration, in light of the above deficiency. Based on the Agency analysis, the duration of the intermediate portion of the test product plume is different from that of the reference product. At the beginning and end sectors, the test product's spray plume duration is within 89-95% of that the reference product, and for most comparisons the observed differences are not statistically significant ($p > 0.05$). On the other hand, for the middle sector, the duration of the intermediate portion of the test product plume is 17-21% shorter than that of the reference product, and the observed differences are highly significant ($p<0.0001$)

These data indicate that, at the middle sector, the intermediate portions of the spray plumes of the test and reference products were maintained for significantly different durations. The Agency is uncertain regarding the impact of the observed difference in duration of the intermediate portion of the test and reference spray plumes upon D50 values. This may be a contributing factor to the

observed difference in the test and reference product D50 values at the middle sector.

Due to lack of equivalence of the test and reference product with regard to droplet size distribution, your application remains incomplete from the bioequivalence viewpoint. You may repeat the laser diffraction analysis and submit the revised data to support equivalence of droplet size distribution. The revised data should be accompanied by the SOP used and representative (≥ 20%) plots of obscuration/transmission vs. time (msec).

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #75-499
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MHM 1/17/02
HFD-658/ Bio team Leader B. Davit 1/17/02
HFD-655/ Bio GJP Singh GJPS 1-17-02
HFD-650/ D. Conner for 2/27/2002

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Printed in final on 1/17/02

BIOEQUIVALENCY - DEFICIENCIES Submission Date: 11-~~27~~29-01

1. STUDY AMENDMENT (STA) Strengths: 10 mg/mL
Outcome: IC

Outcome Decisions: IC - Incomplete

APPEARS THIS WAY
ON ORIGINAL

Butorphanol Tartrate
Nasal Spray, 10 mg/mL
ANDA #75-499
Reviewer: Moheb H. Makary
W 75499A0402.doc

Novex Pharma
Richmond Hill, Ontario
Submission Dates:
April 5, 2002
~~April 26, 2002~~
~~April 29, 2002~~ (E)

Review of an Amendment

I. Objective:

The firm has submitted its response to the comment made by the Division of Bioequivalence (DBE) in its letter of March 1, 2002).

DBE Comment

Droplet size distribution

Evaluation of equivalence of D50 and SPAN data is based on the intermediate portion of the test and reference product sprays, as it represents the stable portion of the plume. For the middle sector of the product life, the test/reference geometric mean ratios for D50 are outside the 0.90-1.11 range, used by Division of Bioequivalence for acceptance of D50 data for nasal spray products. For the middle sector, the test failed to meet the 0.9-1.11 range at all three distances (3, 5 and 8 cm). Therefore, test product D50 is not equivalent to the reference product D50. The firm was asked to submit the spray plume duration data.

Firm's Response

Novex indicated that after reviewing the collection of the previously submitted D50 droplet size distribution data, it was noticed that the data at the middle sector of the product life were obtained after a period of non-use (overnight). The firm stated that its product requires only one (1) spray to reprime, as demonstrated by the previously submitted repriming data. For this reason, and to conserve product sprays for other analyses, only one spray was used to reprime both the test and reference listed drug (RLD) products. Upon further evaluation of the repriming data submitted for the RLD, the firm realized that the RLD requires two (2) sprays to reprime which might be the factor contributing to the observed differences in D50 values and spray duration.

The firm repeated the droplet size distribution testing and submitted D10, D50, D90 and SPAN data.

Novex Pharma's Butorphanol Nasal Spray, 10 mg/mL, consisted of one lot of the drug solution formulation (Lot #1X260), Lot size ——) divided into three sublots using three separate batches of pumps (Novex Pharma QC Nos. 5325, 4406 and 5806). Butorphanol Nasal Spray, 10 mg/mL, Lot #1X260, is the same lot been used in the previous droplet size distribution testing.

The firm indicated that it did not have sufficient quantities from three lots of the RLD to complete the required repeat testing. It used five bottles from each of Lot Nos. 0J30529 and 0H29692, ten (10) bottles from Lot No. 9F5910, four (4) bottles from Lot No. 0L31505 and six (6) bottles from Lot No. M8K050B, for a total of 30 bottles of the RLD.

On April 25, 2002 the firm was asked to provide the expiration dates for the 5 lots of reference product used in the Droplet Size Distribution testing. On April 26, 2002 the firm submitted the following expiration dates:

Lot Nos.	Number of Bottles	Expiry Date
M8K050B	6	December/00
9F5910	10	June/01
0H29692	5	August/02
0J30529	5	September/02
0L31505	4	November/02

Each unit of the test and reference products was tested at beginning, middle, and end sectors of unit life. At each sector of unit life, each unit was actuated at three distances (3 cm, 5 cm, and 8 cm) relative to the ——— laser beam.

Bioequivalence evaluation is based on D50 and SPAN data. A summary of these data based on the reviewer's calculations is given in Table I.

Table I
Droplet Size Distribution (D50 Data) - Test Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo	p
TEST	BEG	3	Initial	43.63	9.6-12.1	5.36	11.74	1.01	1.02	0.71
		3	Intermediate	37.38	7.0-10.3	9.36	11.30	1.05	1.05	0.07
		3	End	95.74	15.2-18.4	9.03	18.10	1.11	1.13	0.06
		5	Initial	41.66	8.7-10.4	3.91	9.75	1.00	1.00	0.93
		5	Intermediate	36.30	6.0-9.1	3.48	7.68	1.00	1.00	0.83
		5	End	62.50	16.6-26.9	20.40	26.34	1.07	1.07	0.29
		8	Initial	46.77	6.8-9.6	0.59	7.78	0.98	0.98	0.41
		8	Intermediate	41.73	4.3-6.2	0.76	5.00	0.97	0.97	0.05
		8	End	48.43	3.9-6.8	4.53	6.79	0.97	0.97	0.16
	MIDDLE	3	Initial	45.56	7.4-13.0	7.00	12.94	1.03	1.03	0.34
		3	Intermediate	37.21	5.5-7.2	6.18	11.12	1.03	1.03	0.34
		3	End	90.83	18.4-22.9	16.24	21.64	1.10	1.10	0.07
		5	Initial	41.94	7.4-13.0	4.05	10.44	1.01	1.01	0.76
		5	Intermediate	36.01	5.5-7.2	2.66	6.79	0.99	0.99	0.48
		5	End	58.59	18.4-22.9	21.17	26.37	1.10	1.09	0.19
		8	Initial	46.75	5.5-10.1	3.04	8.05	0.98	0.98	0.44
		8	Intermediate	41.50	3.1-5.9	1.14	4.79	0.97	0.98	0.08
		8	End	46.38	4.4-6.3	2.11	5.79	0.95	0.95	0.00
	END	3	Initial	44.88	10.8-12.6	7.07	12.88	1.02	1.02	0.56
		3	Intermediate	36.27	8.0-11.5	5.91	10.37	1.02	1.02	0.46
		3	End	81.95	17.8-25.0	11.48	21.79	1.09	1.09	0.15
		5	Initial	42.03	3.2-13.7	4.80	11.07	1.00	1.00	0.94
		5	Intermediate	36.00	4.7-7.2	3.00	6.68	0.99	0.99	0.43
		5	End	53.30	16.9-20.5	18.76	24.51	1.05	1.05	0.49
		8	Initial	46.82	6.8-10.5	2.25	8.60	0.99	0.99	0.51
		8	Intermediate	41.47	3.4-6.3	0.65	4.97	0.97	0.97	0.05
		8	End	46.24	3.5-5.8	0.76	4.57	0.97	0.97	0.05

Droplet Size Distribution (D50 Data) - REF Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
REF	BEG	3	Initial	43.14	10.7-16.2	9.56	14.74
		3	Intermediate	35.76	9.8-13.2	9.11	13.42
		3	End	86.19	14.7-31.7	14.62	26.36
		5	Initial	41.56	7.3-11.1	6.43	10.32
		5	Intermediate	36.45	6.0-9.0	3.76	8.24
		5	End	58.25	16.4-37.1	8.35	28.58
		8	Initial	47.61	5.5-10.8	3.03	8.02
		8	Intermediate	42.98	4.3-9.7	0.45	6.65
		8	End	50.01	9.1-11.3	3.64	10.08
	MIDDLE	3	Initial	44.21	10.2-12.4	10.78	13.64
		3	Intermediate	36.20	9.0-12.5	11.41	13.54
		3	End	82.64	13.0-34.0	4.73	23.00
		5	Initial	41.59	6.6-9.8	4.81	9.40
		5	Intermediate	36.49	6.1-7.9	2.86	7.33
		5	End	53.41	18.3-31.0	6.85	23.90
		8	Initial	47.50	6.2-11.9	1.74	8.59
		8	Intermediate	42.57	4.8-9.8	0.61	6.70
		8	End	48.66	4.5-11.8	4.92	8.71
	END	3	Initial	44.37	11.6-15.9	9.12	14.78
		3	Intermediate	35.74	8.9-12.0	8.82	12.44
		3	End	77.32	14.9-25.0	5.99	21.51
		5	Initial	42.12	6.7-11.9	5.58	10.57
		5	Intermediate	36.53	6.3-9.4	2.94	8.30
		5	End	50.90	11.7-34.7	11.76	26.99
		8	Initial	47.43	4.6-10.7	1.84	7.36
		8	Intermediate	42.72	4.4-10.7	1.44	7.13
		8	End	47.74	3.8-9.4	3.92	7.55

Droplet Size Distribution (SPAN Data) - Test Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo	p
TEST	BEG	3	Initial	1.79	4.6-7.7	1.79	6.00	0.95	0.96	0.05
		3	Intermediate	1.93	3.2-8.3	1.93	6.88	0.96	0.96	0.07
		3	End	1.91	16.9-17.9	1.92	18.66	0.94	0.94	0.19
		5	Initial	1.71	6.8-9.2	4.05	8.89	1.03	1.04	0.25
		5	Intermediate	1.71	6.4-15.6	4.22	10.95	1.01	1.02	0.87
		5	End	2.74	14.9-15.4	14.81	20.12	0.98	0.98	0.73
		8	Initial	1.38	5.6-7.9	3.43	7.06	1.00	1.00	0.95
		8	Intermediate	1.30	4.9-7.0	4.65	7.29	1.02	1.03	0.59
		8	End	2.59	3.0-25.8	13.78	21.04	1.17	1.19	0.02
	MIDDLE	3	Initial	1.79	5.5-10.6	3.64	8.40	0.95	0.96	0.11
		3	Intermediate	1.93	4.9-6.3	3.16	6.05	0.95	0.95	0.05
		3	End	2.01	11.7-21.9	12.49	18.87	0.95	0.95	0.23
		5	Initial	1.69	3.6-13.4	3.36	8.52	1.01	1.01	0.77
		5	Intermediate	1.70	5.1-16.4	4.44	10.30	1.00	1.01	0.96
		5	End	2.92	14.9-15.5	13.01	18.40	0.97	0.97	0.57
		8	Initial	1.37	4.4-8.1	2.94	6.83	1.01	1.02	0.52
		8	Intermediate	1.29	4.7-8.9	4.26	7.45	1.02	1.02	0.52
		8	End	2.65	12.6-18.5	10.43	17.45	1.25	1.29	0.00
	END	3	Initial	1.78	5.0-8.6	0.86	6.50	0.94	0.95	0.02
		3	Intermediate	1.92	3.4-10.5	3.65	7.55	0.93	0.93	0.00
		3	End	2.18	14.2-25.5	7.92	20.96	0.97	0.93	0.56
		5	Initial	1.67	3.7-10.4	0.35	6.76	1.00	1.01	0.86
		5	Intermediate	1.69	5.1-13.9	5.74	9.77	1.02	1.03	0.53
		5	End	3.11	12.6-17.1	10.10	16.27	1.03	1.03	0.52
		8	Initial	1.38	4.8-11.5	1.10	7.61	1.02	1.02	0.52
		8	Intermediate	1.29	4.4-10.0	5.43	8.33	1.01	1.02	0.77
		8	End	2.52	9.4-26.3	17.06	23.57	1.17	1.20	0.02

Droplet Size Distribution (SPAN Data) - REF Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
REF	BEG	3	Initial	1.88	9.5-15.1	1.34	12.24
		3	Intermediate	2.02	9.7-12.8	0.57	10.82
		3	End	2.04	14.5-23.1	12.50	22.55
		5	Initial	1.66	11.7-18.5	4.70	14.47
		5	Intermediate	1.70	15.2-20.7	9.47	19.20
		5	End	2.79	15.2-24.4	1.80	18.34
		8	Initial	1.38	10.1-14.1	6.83	13.78
		8	Intermediate	1.27	12.4-19.4	8.45	17.87
		8	End	2.22	15.9-35.0	12.39	27.09
	MIDDLE	3	Initial	1.88	8.7-14.4	5.24	12.17
		3	Intermediate	2.04	9.9-14.5	2.73	12.23
		3	End	2.12	12.0-26.0	7.97	19.45
		5	Initial	1.68	12.2-16.7	3.62	13.76
		5	Intermediate	1.70	13.0-22.3	9.94	17.96
		5	End	3.00	14.3-19.0	3.08	15.83
		8	Initial	1.35	10.7-11.1	3.79	10.99
		8	Intermediate	1.27	9.7-15.3	6.82	14.17
		8	End	2.11	21.6-37.7	13.03	28.18
	END	3	Initial	1.89	8.3-15.2	4.10	12.91
		3	Intermediate	2.07	10.0-13.7	2.96	11.39
		3	End	2.24	11.4-22.1	7.09	18.61
		5	Initial	1.67	10.7-15.1	5.11	12.70
		5	Intermediate	1.66	12.2-15.4	9.47	16.05
		5	End	3.02	9.7-22.8	5.69	15.57
		8	Initial	1.36	8.2-15.2	8.09	13.36
		8	Intermediate	1.28	9.4-16.1	7.53	15.04
		8	End	2.16	28.3-38.5	8.23	32.21

Comments on Droplet Size Distribution

1. The ratios of the test geometric means to the reference geometric means for D50 at initial, and end of plume formation are within 0.98-1.03 and 0.95-1.13 range, respectively. Based on the reviewer's survey of computer printouts, transmission of laser light was most obscured at the intermediate plume formation and it was the least at the end. Therefore, the reviewer considers that the concentration of droplets was highest at the middle of plume formation. At that stage the ratio was between 0.97 to 1.05. For most comparisons the P values were insignificant.

2. The ratios of the test geometric means to the reference geometric means for SPAN at initial (onset) and end of plume formation are within 0.95-1.04 and 0.93-1.29 range, respectively. At middle of plume formation the ratio was between 0.93 to 1.03. For most of the comparisons the P values were insignificant.

3. For D50 and SPAN, the total variability at the initial, middle, and end of plume formation for the test product is comparable or less than that of reference product.

Based on the above data, the ratios of the test geometric means to the reference geometric means for the intermediate plume formation for D50 and SPAN are within the 90-111% limits used by DBE as an acceptance criteria for the solution nasal spray drug products.

However, since the firm used two expired lots of the reference product (lot #M8K050B, EXP. December/2000 and lot #9F5910, EXP. June/2001) at the time of Droplet Size Distribution testing (3/2002). Therefore, the testing results for D50 and SPAN are invalid.

Reply to Comment:

The firm reply to the comment is unacceptable due to the use of certain lots of the reference product beyond the expiry date.

Deficiency Comment:

The firm used two expired lots of the reference product (lot #M8K050B, EXP. December/2000 and lot #9F5910, EXP. June/2001) at the time of Droplet Size Distribution testing (3/2002). Therefore, the testing results for D50 and SPAN are invalid.

II. Recommendation:

The *in vitro* performance testing conducted by Novex Pharma on its Butorphanol Tartrate Nasal Spray, 10 mg/mL comparing it with the reference product, Stadol®, nasal solution (Bristol-Myers) has been found incomplete for the reason given in deficiency comment.

Moheb H. Makary

Moheb H. Makary, Ph.D. Date: 5/2/02
Review Branch III
Division of Bioequivalence

for RD INITIALLED ZWAHBA
FT INITIALLED ZWAHBA Date: 5/2/02

Concur: Dale P. Conner Date: 5/2/02
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/4-29-2002, 5-2-02, 75499A0402.doc
cc: ANDA #75-499, original, HFD-658 (Makary), Drug File, Division File.

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-499 APPLICANT: Novex Pharma

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

You used two expired lots of the reference product (lot #M8K050B, EXP. December/2000 and lot #9F5910, EXP. June/2001) at the time of Droplet Size Distribution testing (3/2002). Therefore, the testing results for D50 and SPAN are invalid.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75-499
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader Z. Wahba

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Printed in final on 5/2/02

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MMM 5/2/02
HFD-658/ Bio team Leader Z. Wahba CW 5/2/02
HFD-655/ Bio GJP Singh GOPS 5-2-02
HFD-650/ D. Conner DMC 5/2/02

BIOEQUIVALENCY - DEFICIENCIES Submission Date:4-5-02

1. STUDY AMENDMENT (STA) Strengths: 10 mg/mL
Outcome: IC

Outcome Decisions: IC - Incomplete

~~2. Study Amendment (STA) 4-26-02 Strengths: 10 mg/mL~~
~~4-29-02~~
~~Outcome: WC~~
~~(KS) 5/8/02~~

Please make the 4/29/02 submission a new correspondence.

SEP - 6 2002

Butorphanol Tartrate
Nasal Spray, 10 mg/mL
ANDA #75-499
Reviewer: Moheb H. Makary
W 75499STA0802.doc

Novex Pharma
Richmond Hill, Ontario
Submission Dates:
August 12, 2002

Review of an Amendment

I. Objective:

The firm has submitted its response to the comment made by the Division of Bioequivalence (DBE) in its letter of May 9, 2002).

DBE Comment

The firm used two expired lots of the reference product (lot #M8K050B, EXP. December/2000 and lot #9F5910, EXP. June/2001) at the time of Droplet Size Distribution testing (3/2002). Therefore, the testing results for D50 and SPAN are invalid.

Firm's Response

The firm repeated the Droplet Size Distribution analysis using three unexpired lots of the reference product.

The lot Nos. and expiry dates of the reference product tested are given below:

Lot Nos.	Number of Bottles	Expiry Date
1F43643	10	June 2003
1F43639	10	June 2003
1C52465	10	March 2003

Novex Pharma's Butorphanol Nasal Spray, 10 mg/mL, consisted of one lot of the drug solution formulation (Lot #1X260), Lot size ——) divided into three sublots using three separate batches of pumps (Novex Pharma QC Nos. GE1527, GE1542 and GE1547). Butorphanol Nasal Spray, 10 mg/mL, Lot #1X260, is the same lot been used in the previous droplet size distribution testing.

Each unit of the test and reference products was tested at beginning, middle, and end sectors of unit life. At each sector of unit life, each unit was actuated at three

distances (3 cm, 5 cm, and 8 cm) relative to the [redacted] laser beam.

Bioequivalence evaluation is based on D50 and SPAN data. A summary of these data based on the reviewer's calculations is given in Table I.

Table I
Droplet Size Distribution (D50 Data) - Test Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo Mean(N=30)	p
TEST	BEG	3	Initial	45.57	9.7-15.3	5.18	12.85	1.01	1.01	0.78
		3	Intermediate	36.45	8.2-15.4	4.13	11.22	1.00	1.00	0.91
		3	End	118.91	6.6-14.1	3.61	10.67	1.04	1.04	0.28
		5	Initial	42.92	7.9-11.6	2.53	9.77	1.01	1.01	0.81
		5	Intermediate	36.08	4.2-8.0	2.22	6.40	0.99	0.99	0.45
		5	End	87.15	15.3-20.5	2.78	17.16	1.07	1.09	0.18
		8	Initial	47.20	3.9-7.1	2.30	6.27	0.90	0.99	0.43
		8	Intermediate	41.46	2.3-5.8	0.25	4.96	0.99	0.99	0.25
		8	End	50.73	6.1-9.6	3.91	8.16	0.96	0.97	0.26
	MIDDLE	3	Initial	46.76	8.1-13.3	4.22	11.83	1.02	1.02	0.59
		3	Intermediate	36.12	6.7-14.4	4.28	11.29	0.99	0.99	0.76
		3	End	106.29	16.1-22.8	3.49	18.55	0.98	0.97	0.57
		5	Initial	42.95	7.4-13.0	4.05	10.44	1.00	1.01	0.83
		5	Intermediate	36.19	2.9-8.2	2.49	6.72	0.99	0.99	0.55
		5	End	70.72	17.5-25.3	4.65	21.48	0.95	0.96	0.35
		8	Initial	47.65	5.2-7.1	1.41	6.09	1.00	1.00	0.91
		8	Intermediate	41.38	2.8-6.6	1.16	4.78	0.98	0.98	0.24
		8	End	47.00	4.8-8.5	2.16	6.64	0.98	0.98	0.39
	END	3	Initial	46.55	10.3-12.5	3.15	11.47	1.01	1.01	0.78
		3	Intermediate	35.95	8.6-13.1	3.40	10.52	0.98	0.98	0.57
		3	End	103.97	11.6-17.1	2.68	14.08	1.03	1.04	0.42
		5	Initial	42.96	5.6-10.2	2.13	8.65	1.01	1.01	0.61
		5	Intermediate	36.13	4.0-8.0	2.73	6.94	1.00	0.99	0.79
		5	End	71.95	21.2-27.9	10.69	25.24	1.09	1.10	0.16
		8	Initial	47.98	3.8-7.6	1.52	6.27	1.00	1.00	0.99
		8	Intermediate	41.46	2.8-5.6	1.28	4.40	0.99	0.99	0.26
		8	End	46.10	4.1-7.3	2.34	6.24	0.97	0.97	0.20

Droplet Size Distribution (D50 Data) - REF Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
REF	BEG	3	Initial	45.08	11.8-14.3	3.90	12.86
		3	Intermediate	36.31	11.1-12.5	3.67	11.67
		3	End	114.81	12.9-17.3	1.78	14.21
		5	Initial	42.64	6.8-11.8	1.24	8.94
		5	Intermediate	36.56	6.0-6.7	2.30	6.45
		5	End	81.33	16.7-31.6	7.78	22.93
		8	Initial	47.85	6.0-6.4	1.44	2.91
		8	Intermediate	42.08	4.0-5.8	1.66	2.02
		8	End	52.69	9.8-16.3	7.41	8.06
	MIDDLE	3	Initial	45.91	10.3-16.5	4.89	13.25
		3	Intermediate	36.49	10.8-13.8	4.96	12.43
		3	End	108.99	15.8-19.8	5.64	17.38
		5	Initial	42.75	6.3-11.2	3.88	9.07
		5	Intermediate	36.57	4.9-8.5	2.98	6.87
		5	End	74.62	27.1-28.6	6.83	27.47
		8	Initial	47.55	4.9-7.5	2.35	6.47
		8	Intermediate	42.06	3.0-6.1	2.23	5.11
		8	End	47.88	4.1-9.2	5.32	8.14
	END	3	Initial	46.07	12.8-15.2	4.27	14.01
		3	Intermediate	36.69	10.6-16.9	5.41	14.52
		3	End	101.19	14.2-21.0	4.36	18.09
		5	Initial	42.46	7.0-9.7	2.19	8.23
		5	Intermediate	36.309	4.9-7.5	2.51	6.61
		5	End	65.86	21.9-33.0	10.07	27.94
		8	Initial	47.99	5.5-7.8	2.23	6.62
		8	Intermediate	42.08	5.1-6.3	2.13	5.38
		8	End	47.46	5.7-11.9	1.95	8.98

Droplet Size Distribution (SPAN Data) - Test Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo	p
TEST	BEG	3	Initial	1.84	5.4-9.9	2.88	7.71	0.94	0.94	0.02
		3	Intermediate	2.01	5.7-11.3	1.60	7.99	0.96	0.96	0.08
		3	End	1.51	6.8-16.3	3.76	11.41	0.96	0.97	0.27
		5	Initial	1.75	7.7-12.3	1.14	10.63	0.97	0.97	0.41
		5	Intermediate	1.73	10.2-12.4	2.97	10.94	0.96	0.96	0.31
		5	End	2.04	15.8-21.3	2.21	17.34	0.91	0.93	0.12
		8	Initial	1.38	8.7-12.1	0.42	10.09	0.98	0.98	0.40
		8	Intermediate	1.28	7.5-10.8	0.78	8.80	0.97	0.97	0.28
		8	End	3.03	6.8-6.9	1.90	6.80	1.03	1.03	0.34
	MIDDLE	3	Initial	1.84	6.0-7.6	0.31	6.44	0.96	0.96	0.04
		3	Intermediate	2.01	6.3-9.5	2.51	7.70	0.96	0.96	0.13
		3	End	1.73	13.6-24.6	3.38	18.96	1.02	1.02	0.69
		5	Initial	1.73	8.5-12.4	3.48	10.66	0.96	0.97	0.33
		5	Intermediate	1.71	12.2-14.0	5.20	13.70	0.94	0.95	0.21
		5	End	2.54	14.6-24.1	6.27	21.66	1.02	1.04	0.64
		8	Initial	1.40	6.5-12.5	1.09	10.06	0.99	0.99	0.84
		8	Intermediate	1.30	7.8-12.3	2.31	9.63	0.99	0.99	0.63
		8	End	3.13	7.4-10.6	3.51	9.55	1.05	1.05	0.11
	END	3	Initial	1.85	4.2-9.9	2.70	7.83	0.97	0.97	0.22
		3	Intermediate	2.03	7.3-11.3	1.24	8.99	0.97	0.97	0.21
		3	End	1.76	10.0-15.5	2.81	13.54	0.96	0.97	0.27
		5	Initial	1.70	6.5-8.8	2.45	7.50	0.98	0.98	0.86
		5	Intermediate	1.68	11.7-12.7	3.31	12.13	0.96	0.96	0.53
		5	End	2.55	17.1-23.5	10.56	22.56	0.92	0.93	0.52
		8	Initial	1.39	9.4-11.1	2.59	10.07	0.98	0.98	0.58
		8	Intermediate	1.29	7.5-9.1	2.80	8.17	0.97	0.98	0.44
		8	End	3.08	7.2-13.3	5.41	10.19	1.03	1.04	0.32

Droplet Size Distribution (SPAN Data) - REF Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
REF	BEG	3	Initial	1.96	7.3-14.9	2.07	10.66
		3	Intermediate	2.11	8.4-14.3	1.90	11.71
		3	End	1.57	10.4-20.0	2.40	15.50
		5	Initial	1.80	9.1-22.5	1.40	14.98
		5	Intermediate	1.81	11.2-25.1	6.43	18.77
		5	End	2.23	16.2-28.8	10.72	24.44
		8	Initial	1.41	5.8-9.0	2.29	7.96
		8	Intermediate	1.32	7.3-10.5	4.94	9.55
		8	End	2.96	6.7-11.9	5.31	10.89
	MIDDLE	3	Initial	1.93	5.8-11.8	1.50	9.01
		3	Intermediate	2.10	7.1-16.7	1.53	11.63
		3	End	1.70	18.1-21.0	5.39	19.05
		5	Initial	1.80	8.7-22.2	4.19	15.79
		5	Intermediate	1.82	11.3-26.9	7.43	19.67
		5	End	2.48	23.0-29.7	5.94	26.38
		8	Initial	1.40	6.6-14.6	2.06	10.20
		8	Intermediate	1.32	5.6-17.1	3.94	11.60
		8	End	2.98	6.6-14.6	1.68	11.25
	END	3	Initial	1.90	6.2-12.6	0.53	8.88
		3	Intermediate	2.10	7.5-13.4	0.95	10.69
		3	End	1.83	13.2-22.1	3.04	18.92
		5	Initial	1.74	7.8-21.6	5.27	14.83
		5	Intermediate	1.75	8.9-22.4	5.24	15.93
		5	End	2.76	20.5-29.8	9.61	25.09
		8	Initial	1.42	5.3-22.8	4.23	14.64
		8	Intermediate	1.33	8.6-26.4	5.03	17.26
		8	End	2.98	6.4-22.3	1.74	13.67

Comments

1. The ratios of the test geometric means to the reference geometric means for D50 at initial, middle and end of plume formation are within 0.96-1.10. For all the comparisons the P values were insignificant.

2. The ratios of the test geometric means to the reference geometric means for SPAN at initial (onset), middle and end of plume formation are within 0.93-1.05. For most of the comparisons the P values were insignificant.

3. For D50 and SPAN, the total variability at the initial, middle, and end of plume formation for the test product is comparable or less than that of reference product.

4. Based on the above data, the ratios of the test geometric means to the reference geometric means for the intermediate plume formation for D50 and SPAN are within the 90-111% limits used by DBE as an acceptance criteria for the solution nasal spray drug products.

5. Data for all other *in vitro* performance tests have previously been found acceptable (DBE review dates April 20, 2001, February 27, 2002 and May 9, 2002)

Reply to Comment:

The firm reply to the comment is acceptable.

Recommendation:

The *in vitro* performance testing conducted by Novex Pharma on its Butorphanol Tartrate Nasal Spray, 10 mg/mL comparing it with the reference product, Stadol®, nasal solution (Bristol-Myers) has been found to be acceptable by the Division of Bioequivalence. The studies demonstrate equivalent *in vitro* performance of Novex's Butorphanol Tartrate Nasal Spray, 10 mg/mL, and the reference listed drug product Stadol®, Nasal Solution, 10 mg/mL manufactured by Bristol-Myers Squibb.

From the bioequivalence viewpoint, the firm has met the requirements of formulation sameness, device comparability and *in vitro* performance testing.

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED
FT INITIALLED GJP SINGH Gurjaspal Singh Date 8/28/02

Concur: Dale P. Conner Date: 9/6/02
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 8-26-02, 8-28-02, 75499STA0802.doc
cc: ANDA #75-499, original, HFD-658 (Makary), Drug File, Division File.

CC: ANDA #74-499
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary MHM
HFD-658/ Bio team Leader G. Singh

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Printed in final on 8/28/02

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MHM 8
HFD-658/ Bio team Leader G. Singh GJS 8/28/02
HFD-655/ Bio GJP Singh
HFD-650/ D. Conner DPC 9/6/02

BIOEQUIVALENCY - ACCEPTABLE submission date: 8-12-02

1. **STUDY AMENDMENT** (STA) 8/22/00 Strengths: 10 mg/mL
Outcome: AC

Outcome Decisions: **AC - Acceptable**

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-499 APPLICANT: Novex Pharma

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

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

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # :75-499 SPONSOR : Novex Pharma

DRUG AND DOSAGE FORM : Butorphanol Tartrate Nasal Spray

STRENGTH(S) : 10 mg/mL

TYPES OF STUDIES : In Vitro Studies

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : Novex Pharma, Primedica Corporation

STUDY SUMMARY : In Vitro Studies are acceptable.

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic NO	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 8/28/02

TEAM LEADER : GJP SINGH, Ph.D. BRANCH : III

INITIAL : GJP SINGH DATE : 8/28/02

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC **DATE :** 9/6/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

ADMINISTRATIVE DOCUMENTS

A 1.1

TELEPHONE MEMO

To: Marcy Mcdonald (Agent: Apotex Corp.) Novex
(847) 573-9999 EXT. 223

CC: ANDA 75-499 Butorphanol Tartrate Injection USP, 10 mg/mL

From: Saundra T. Middleton

Date: June 19, 2000

Subject: **UN-withdraw** pending ANDA

Background:

On May 16, 2000, OGD sent Novex a letter asking them to respond to the September 9, 1999 NA letter within 10 days or the office may WD the above ANDA.

On June 7, 2000 a WD letter was sent to Novex for not responding within 10 days. Later that day of the 7th, OGD received a letter from Novex, asking for additional time to respond to the NA, the firm stated that they will amend their ANDA by July 30, 2000 (the WD letter was already sent by the mail room).

The ANDA was **UN-Withdrawn** in the COMIS on June 14. 2000.

Ms. Mcdonald was asked to provide a cGMP statement from the applicant "Apotex Corp. "

The above information will be submitted ASAP.

FROM THE DESK OF...

SAUNDRA T. MIDDLETON
CONSUMER SAFETY OFFICER
CDER\FDA\OGD\DLPS
7500 STANDISH PLACE
ROCKVILLE MD 20855

301-827-5862
Fax: 301-594-1174

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-499 Applicant Novex Pharma
Drug Butorphanol Tartrate Nasal Spray Strength 10mg/mL

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

	DRAFT Package	FINAL Package
1. Project Manager, Team 10	Date 11/20/02	Date 11/26/02
Review Support Br Thomas Hunchuck	Initials TH	Initials

Application Summary:

Original Rec'd date Nov. 6 1998
Date Acceptable for Filing Feb 5, 1999 ✓
Patent Certification (type) III
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked NDA#
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def./N/A Minor issued ☐ Date
Comments:

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 3/19/01
Date of Office Bio Review 9/16/02
Date of Labeling Approv. Sum 4/1/02
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

2. Gregg Davis **PPIV ANDAs Only** Date 12/4/02 Date
Supv., Reg. Support Branch Initials Initials

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant II IV → III
Notify patent holder/NDA holder: Yes ☐ No ☐ N/A
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled: N/A
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Comments:

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

RLD: Stadol NS Nasal Spray 10mg/spray
Bristol-Myers Squibb Co.
NDA 19-890
Pharm. Research Institute

There are no unexpired patents or exclusivity listed in the Current Orange Book for this drug product. Novex submitted a paragraph IV patent certification upon submission and later revised it to a P III upon patent expiry.

3. Div. Dir./Deputy Dir. 11/20/02
Chemistry Div. I or II
Comments:

Date 12/3/02
Initials

one satisfactory,

REVIEWER: FINAL ACTION

4. Frank Holcombe
Assoc. Dir. For Chemistry
Date ____
Initials ____
Comments: (First generic drug review)
N/A. This drug product was previously approved for ESI Lederle (ANDA 75-759) and Roxane Laboratories (ANDA 75-824). (MVR)

5. Peter Rickman
Acting Director, DLPS
Date 12/4/02
Initials
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 3/19/01 (Verified 12/4/02) No O.A.I. alerts noted. In vivo Bioequivalence studies found acceptable 8/28/02 Office-Level bio endorsed 9/6/02. FR acceptable 4/1/02 (as endorsed 11/27/02). CMC acceptable 11/25/02. Methods validation completed on the drug product-acceptable. Drug substance (API) is compendial.

~~OR~~

5. Robert L. West
Acting Deputy Director, OGD
Date 12/4/2002
Initials
Para.IV Patent Cert: Yes☐ No☒ Pending Legal Action: Yes☐ No☒ Petition: Yes☐ No☒
Comments: The '378 patent has expired.

This application is recommended for approval

6. Gary Buehler
Director, OGD
Date 12/4/02
Initials GB
Comments:

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Team Lo Tom Hinchliffe
Review Support Branch
Date 12/4/02
Initials
N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
12:00 Time notified of approval by phone 12:30 Time approval letter faxed

FDA Notification:
12/4/02 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/4/02 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

V:\reports\approval\approvrou2.doc

6.1

Record of Telephone Conversation

The following request were made:

1. Please include a procedure to identify known impurities regarding Method TM-767. (e.g. using RRT with specified range: RRT [redacted]) Please, revise the system suitability requirements to provide for a resolution criterion using Butorphanol Tartrate and one of the known impurities, if possible. Otherwise, specify the RT for Butorphanol Tartrate.

2. Revise the Additional Shelf-Life Stability Protocol to indicate that the stability studies will be performed with pumps from three different lots.

3. Explain how the expiration dating period is calculated.

4. Commit to perform the priming/re-priming requirement and drug delivery studies based on SCU and other parameters with drug product stored in horizontal orientation after different periods of non-use using the validation batch with Pump B to support the proposed labeling insert.

Addendum on November 5, 2001 with Jen Docherty:

In addition to the above comments, please certify that your package system meets the requirements found in 21 CFR 1302.06.

Date:
November 1, 2001

ANDA Number:
75-499

Product Name:
Butorphanol Tartrate Nasal Spray

Firm Name:
Novex

Firm Representative:
Rahsmi Amin (US Agent)

Phone Number:
847-573-9999 X223

FDA Representative:
Jeen Min
Tao-Chin Wang

Signatures:

Jeen Min
11/5/01

CC: ANDA 75-499

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

CORRESPONDENCE

RTF 314.10(a)(3) S. Middleton 12-7-98

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

November 4, 1998

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Butorphanol Tartrate Nasal Spray 10 mg/mL
Original Submission

Dear Mr. Sporn:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex, Inc., is submitting, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act as amended September 24, 1984, an abbreviated new drug application for Butorphanol Tartrate Nasal Spray 10 mg/mL.

We are submitting an archival copy under blue cover, a chemistry review copy under red cover, a field copy under burgundy cover and the bioavailability/bioequivalence review section under orange cover. As this product is not USP, we are submitting two additional copies of the analytical section.

We appreciate your review of this application. Please direct any inquiries regarding this application to me at the address listed.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

NOV 06 1998

J:\ANDA\BUTOR SPRAY\SUBLTRS.DOC

ANDA 75-499

Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy Macdonald
50 Lakeview Parkway
Suite 127
Vernon Hills, IL 60061

DEC 8 1998

Dear Madam:

Please refer to your abbreviated new drug application 75-499 dated November 4, 1998 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 1 mg/spray.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

You are required to conduct studies on the basis of comparable *in vitro* performance of the test and reference product. You are advised to submit a protocol testing for three batches of the reference listed drug, and if available, for more than one batch of the test product to the Office. The following testing should be considered:

unit dose
spray pattern
plume geometry
droplet size distribution by laser diffraction (pivotal) and cascade impactor (three data sets summing to mass balance: atomizing chamber plus separator, if used; S0 - stage above 5 microns; drug from 5 microns - filter)
Priming
tail off

If you have any questions regarding this issue, please contact Nasser Mahmud, Project Manager, in the Division of Bioequivalence at (301) 827-5847.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

You have failed to address any marketing exclusivity that may exist for the above product.

Please revise your components and composition statement to read g/L instead of g/mL (page 91).

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call.

Saundra T. Middleton
Project Manager
(301) 827-5862

Sincerely yours,

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-499
DUP/Jacket
Division File
Field Copy
HFD-330
HFD-82
HFD-610/BWest
HFD-615/MBennett

Endorsements:
HFD-615/Rickman, Chief, RSB
HFD-615/SMiddleton, CSO date/ 12-7-98
HFD-647/UVenkataram, Sup. Chemistry\ date/
X:\NEW\FIRMSNZ\NOVEX\LTRS&REV\75499.RTF
F/T by njg 11/30/98
ANDA Refuse to File!

APPEARS THIS WAY
ON ORIGINAL

Ack for filing
2/11/99
S. Middleton

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

January 28, 1999

NDA ORIG AMENDMENT
Ac

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

REFUSAL TO FILE RESPONSE

RE: ANDA 75-499
Butorphanol Tartrate Nasal Spray 10 mg/mL

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby submitting (in duplicate) this response to the Refusal to File letter dated December 8, 1998.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

RECEIVED
FEB 02 1999
GENERIC DRUGS

ANDA 75-499

Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy Macdonald
50 Lakeview Parkway
Suite 127
Vernon Hills, IL 60061

FEB 26 1999

Dear Madam:

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

Reference is also made to our "Refuse to File" letter dated December 8, 1998 and your amendment dated January 28, 1999.

NAME OF DRUG: Butorphanol Tartrate Nasal Spray, 1 mg/spray

DATE OF APPLICATION: November 4, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: Feburary 2, 1999

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative

designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b),provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

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,

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-499
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-610/R. West
HFD-330
HFD-92
HFD-615/M.Bennett

Endorsements: HFD-615/PRickman, Chief, RSB date 2/25/99
HFD-615/SMiddleton, CSO S. Middleton date 2/16/99
HFD-647/UVenkataram, Sup. Chem. date
V:\FIRMSNZ\NOVEX\LTRS&REV\75499.ACK
F/T by mjl/2/16/99
ANDA Acknowledgment Letter!

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

May 18, 1999

NEW CORRESP.
NC

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

Dear Sir/Madam:

Re: Revised Patent Certification for
BUTORPHANOL TARTRATE NASAL SOLUTION, 10 mg/mL
ANDA No. 75-499

Would you please advise if Novex Pharma is the first company to file with a Paragraph IV Certification?

Please contact me directly at (905) 884-2050 or FAX me at (905) 884-0422.

Yours sincerely,
Novex Pharma

A. van Doornik
Senior Vice President
Scientific Affairs

/kc

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 26 1999
OGD

ISO 9002 REGISTERED COMPANY SGS

BIOEQUIVALENCY AMENDMENT

JUN - 7 1999

ANDA 75-499

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Novex Pharma PHONE: 847-573-9999 x223

ATTN: Marcy MacDonald FAX: 905-884-0357

FROM: Patty Nguyen PROJECT MANAGER (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on January 25, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 10 mg/mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 5 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

PMSB 6/4/99

X:\new\ogdadmin\glossary\biofax.frm

JUN - 7 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-499 APPLICANT: Novex Pharma

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has the following comments:

1.1 Unit dose and uniformity of unit dose

Consistent with the Potency Test described in the 27 June 1989 Division of Bioequivalence Guidance for the "In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)", this test should be performed at beginning, middle, and end of use life of the product after product priming.

For Butorphanol Tartrate Nasal Spray, a dose is one spray (1 mg). The amount of drug per single spray (not the mean of two or more consecutive sprays) should be determined using a validated stability-indicating biochemical/chromatographic assay. In addition to the chemical assay of drug per spray, measurement of spray weight is also requested. Please clarify the unit weight in Figure 5.

1.2 Spray Pattern

Spray patterns should be determined at three distances from the TLC plate at beginning and end life sectors. Spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug-specific reagent. A drug-specific reagent will not develop color when tested with placebo. Photographs of spray patterns, in color if appropriate, should be analyzed to measure the shortest (D_{min}) and widest (D_{max}) diameters. Reported data should include values of D_{min}, D_{max} and ovality ratio (D_{max}/D_{min}), along with photographs and markings indicating D_{min} and D_{max}.

1.3 Plume Geometry

Plume geometry describes two side views, at a 90^0 angle to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. Please provide plume geometry based on high speed photography. Plume geometry may be performed only at beginning of use life. Plumes should be characterized at three or more delay times after actuation. These times should be chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time. Photographs of spray plumes should be used to measure plume length, plume width, and plume (spray cone) angle. Please provide all photographs and data characterizing plume dimensions including scaling information to indicate actual size.

1.4 Droplet size distribution

a. Laser Diffraction: Droplet size distribution by laser diffraction (e.g. ———————) should be determined at the beginning, middle, and end of use life of the product. Measurements should be made at three distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. Please report the data in the form of D_{10}, D_{50}, D_{90} and SPAN $[(D_{90}-D_{10}/D_{50})]$. Please report the data based on mass (volume). Please submit all instrument/computer printouts, including cumulative percent undersize tables and histograms of particle size distribution. Obscuration should be reported for each run, along with the instrument manufacturer's recommended obscuration ranges.

b. Cascade impaction: The cascade impactor characterizes particles in a smaller size range than the expected range for aqueous nasal sprays. However, it is useful as to assure that there is not an excess mass of "fines" in the test product relative to the RLD. Cascade impactor ———— data should account for mass balance and be reported in the following groups:

Group-1: From valve stem and actuator up to top stage (stage zero).
Group-2: One stage below the top stage.
Group-3: Everything from 2nd stage through the filter.

Because the purpose of the cascade impactor for the aqueous nasal sprays is to characterize fines only, not to provide a particle size distribution, please provide cascade impactor studies only at the beginning and end of canister through-life testing.

c. Other methods: You may wish to provide comparative data by additional methods such as time-of-flight laser.

1.5 PRIMING, LOSS OF PRIME, AND TAIL OFF

Priming: The reference listed drug's patient package insert indicates that up to 7-8 actuations are required to prime. Please submit data to support the statement that the test product requires no more actuations to prime than does the reference product.

Loss of Prime: The reference listed drug's patient package insert indicates that it must be primed by wasting 1-2 sprays, if not used for 48 hours or longer. Please submit comparative data for similar performance characteristics of the test and reference products.

Tail Off: Please submit evidence for comparable tail off characteristics.

Priming, loss of prime and tail off data should be based on the amount of drug per actuation using a biochemical/chromatographic assay. Because the product is labeled to deliver only 14-15 doses, you may combine determination of priming, uniformity of unit dose and tail off in single studies in which drug content in all successive individual actuations (from the first unprimed dose to depletion) is quantitated.

1.6 For all the above comparative *in vitro* tests

a. Pumps should be actuated mechanically to increase reproducibility.

b. No fewer than 10 units (i.e., 10 bottles and associated delivery devices) each of the test and reference products should be tested in a blinded manner.

c. For all *in vitro* tests, you may wish to submit data from three batches of the reference product, and three batches of the test product. However, for the test product you may submit data from a single batch of the solution with a split fill into three equal size sublots, with each sublot prepared from different batches of test product devices (pump and actuator). Batch records for all batches of the test product should be submitted.

d. Please submit SOP's for all tests effective at the time of testing. SOP's should describe the mechanical actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s). Blinding must not interfere with pump performance.

e. Please submit raw data for all tests in the form of paper copies as well as electronic files (Excel 5.0 spread sheets).

f. For tests performed at the beginning (B), middle (M), and end (E) or B and E of use life sectors, equivalence will be assessed at each sector.

2. Metering Devices

The device and the formulation are integral components of a nasal spray. To support sameness of test and reference devices, please provide to the extent possible a side-by-side comparison of the pumps (including diptube length) and actuators used in the test and reference products. This information includes the manufacturer, model numbers of the pumps and actuators, and model numbers of actuator inserts and the overcaps. Please submit technical drawings with dimensions for both the test and reference products, if available.

3. You may wish to consider conducting an acceptable *in vivo* bioequivalence study as a condition for approval of the test product instead of submitting the above mentioned comparative *in vitro* tests. In such case the *in vivo* pharmacokinetic data will be used for evaluation of bioequivalence.

Sincerely yours,

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

June 8, 1999

Noted in NAE
US mail used -
Nancy Meardon 6/11/99

NEW CORRESP
N/C

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA #75-499
Butorphanol Tartrate Nasal Spray
1 mg/spray

To Whom It May Concern:

As required by the accepted for filing letter dated February 26, 1999, Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex, Inc., in accordance with 21 CFR 314.95(b), hereby certifies that a notice has been provided to each patent holder identified under 314.95(a) and that the notice met the content requirements under 314.95(c).

In addition, as per 21 CFR 314.95(e), we are providing documentation of receipt of notice by providing a copy of the return receipt card acknowledging receipt by each person provided the notice. The acknowledgement follows.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

July 21, 1999

NEW CORRESP
Nc

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

CORRECTED INFORMATION

RE: ANDA 75-499
Butorphanol Tartrate Nasal Spray 10 mg/mL

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby submitting a correction to the Refusal to File Response dated January 25, 1999.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

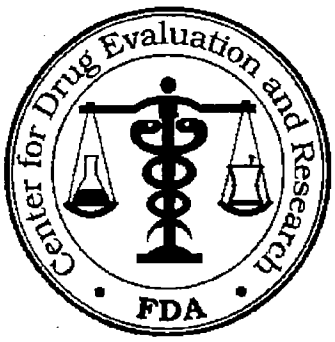
Marcy Macdonald (KK)
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 23 1999
OGD

MAJOR AMENDMENT

ANDA 75-499

SEP - 9 1999



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Novex Pharma PHONE: 847-573-9999

ATTN: Marcy McDonald, Agent FAX: 847-573-1001

FROM: Mark Anderson PROJECT MANAGER (301) 827–5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 4, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 10 mg/mL.

Reference is also made to your amendment dated January 28, 1999.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (20 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

Chemistry and labeling comments are provided.

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MA

Redacted 5 page(s)

of trade secret and/or

confidential commercial

information from

9/9/1999 FDA FAX

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

ANDA Number: **75-499** Dates of Submission: **November 3, 1998 and January 28, 1999**

Applicant's Name: **Novex Pharma**

Established Name: **Butorphanol Tartrate Nasal Spray, 1 mg/spray 10 mg/mL 2.5 mL**

Labeling Deficiencies:

1. CONTAINER 2.5 mL

   a. We note that your storage recommendations on the container label are "Store between 59°-86°F (15°-30°C)" while in your insert there is "Store ———. Please revise to read "Store below 25°C (77°F)".

   b. Please include the controlled substance symbol on the main panel. We refer you to 21 CFR 1302.04 for guidance.

2. PATIENT INSTRUCTIONS

   Satisfactory, in draft.

3. MEDICATION GUIDE

   Please note that as of June 16, 1998 the reference listed drug provides for a patient medication guide for this drug product. You must also submit this labeling piece to your application. We have included a copy of the approval letter for this piece as well as a copy of the medication guide. The text of this medication guide must also appear at the end of the insert labeling and must be referred to in the PRECAUTIONS, Information for Patients subsection. See 21 CFR 201.57(f)(2) for guidance.

4. INSERT

   a. GENERAL COMMENTS

      i. This review was based on the labeling for STADOL NS (BMS, approved April 16, 1999).

ii. Please be consistent with the formatting of your subsection titles. Some are of the same prominence as the section titles.

iii. Use "to" rather than a hyphen when expressing a range of values.

b. TITLE

Include the controlled substance symbol with the title.

c. DESCRIPTION

i. Chemical name - ... (cyclo... [delete hyphen]

ii. Revise the molecular weight to be "477.56".

iii. "1 mg" rather than "1.0 mg".

d. CLINICAL PHARMACOLOGY

i. General Pharmacology and Mechanism of Action, first sentence - 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.

ii. Pharmacodynamics, second sentence - ... within 15 minutes for intramuscular ...

iii. Table 1 - Improve the legibility of the superscripts in this table.

iv. Pharmacokinetics

A). Sixth paragraph - ... and Nursing Mothers under PRECAUTIONS).

B). Paragraph beginning "The major ..."

1). Second sentence - ... 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 (≅ 5-fold) occurs when butorphanol is dosed to steady state (1 mg transnasally q6h for 5 days).

2). Delete the last sentence.

C). Paragraph beginning "About 5% ..." - Delete

D). Last sentence - ... refer to **PRECAUTIONS: Hepatic and Renal Disease, Drug Interactions,** and **Geriatric Use** sections and to **the CLINICAL PHARMACOLOGY, Individualization of Dosage** section below.

v. Clinical Trials, second sentence - ... tartrate injection (This revision should be made in general.)

vi. Postoperative ——————

A). Retitle this "Postoperative Pain".

B). First paragraph, last sentence - "40 mg"

C). Third paragraph, penultimate sentence - "analgesic" rather than "analgesia" (second occurrence)

D). Last sentence - "(2.6 hours)"

vii. Delete the "Preanesthetic Medication", "Balanced Anesthesia" and "Labor" subsections.

viii. Individualization of Dosage

A). Delete the first and third paragraphs.

B). Paragraph beginning "The initial dose ..."

"... in 3 to 4 hours as required <u>after the second dose</u> of the sequence."

e. WARNINGS

Add the following subsections after the second paragraph:

Drug Abuse and Dependence

Drug Abuse

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

Physical Dependence, Tolerance and Withdrawal

Prolonged, continuous use of butorphanol tartrate may result in physical dependence or tolerance (a decrease in response to a given dose). Abrupt cessation of use by patients with physical dependence may result in symptoms of withdrawal.

Note - Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical dependence (see DRUG ABUSE AND

DEPENDENCE section below).

f. PRECAUTIONS

i. Hepatic and Renal Disease

Last sentence - ... (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

ii. Cardiovascular Effects - Relocate "(see CLINICAL PHARMACOLOGY) to the end of the first paragraph.

iii. Use in Ambulatory Patients

A). Relocate this subsection to be after the "Cardiovascular Effects" subsection.

B). Revise this subsection as follows:

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 ... 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. Butorphanol is one of a class of drugs known to be abused and thus should be handled accordingly (see **DRUG ABUSE AND DEPENDENCE** section).
4. Patients should be instructed on the proper use of butorphanol nasal spray (See PATIENT INSTRUCTIONS).

iv. Drug Interactions

A). Add the following as the second paragraph:

In healthy volunteers, the pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol tartrate nasal spray were not affected by the coadministration of a single

6 mg subcutaneous dose of sumatriptan.

B). Add the following as the third paragraph:

The pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol nasal spray were not affected by the co-administration of cimetidine (300 mg QID). Conversely, the administration of butorphanol nasal spray (1 mg butorphanol QID) did not alter the pharmacokinetics of a 300 mg dose of cimetidine.

C). Fourth paragraph (formerly second), first sentence - ... altered by other concomitant ... of drugs (erythromycin ...

v. Information for Patients

A). Relocate this subsection to immediately follow the "Drug Interactions" subsection.

B). Revise the text of this subsection heading to read: Information for Patients (See PRECAUTIONS, Use in Ambulatory Patients.) and delete the remaining text.

C). Please reference the MEDICATION GUIDE and the Patient Instructions in this subsection. See 21 CFR 201.57(f)(2).

vi. Carcinogenesis, Mutagenesis, Impairment of Fertility

A). Revise the first paragraph to read as follows:

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.

B). "m^2" rather than "sq.m."

vii. Pregnancy -

A). See (f)(vi)(B) above.

B). First paragraph, third sentence -

... 30 mg/kg/oral (360 mg/m^2) and 60 mg/kg/oral (720 mg/m^2) also ...

C). Second paragraph - Delete "[redacted]" (two instances).

viii. Labor and Delivery, first paragraph

A). First sentence

1). There have ... (delete [redacted]).

2). ... during labor. The reports ...

B). Last sentence - ... pregnancies. (See OVERDOSAGE, Treatment)

ix. Nursing Mothers, second sentence - "mcg/L" rather than "microgram/liter"

x. Geriatric Use

A). First paragraph, last sentence - ... (see CLINICAL PHARMACOLOGY, Individualization ...

B). Second paragraph, first sentence - ... 65 years. Elderly ...

g. ADVERSE REACTIONS

i. First paragraph, second sentence - ... remainder receiving butorphanol ...

ii. Second paragraph - ... by any route. There ...

iii. Third paragraph, second sentence - Delete [redacted]

iv. Fourth paragraph

A). ... or greater in clinical trials, and were ...

B). Delete the asterisks, the capitalization, and the parenthetical percentages in this subsection

C). Special Senses - Delete "[redacted]".

D). Delete "[redacted]"

v. The following adverse experiences were reported with a frequency of less than 1% in clinical trials, and were ..."

vi. Nervous - ... agitation, dysphoria, hallucinations, hostility, withdrawal symptoms

vii. Delete "[redacted]."
(two instances)

viii. Paragraph beginning "The following infrequent ...

First sentence - ... and under circumstances ...

ix. Cardiovascular - chest pain, hypertension, tachycardia

x. Nervous - Delete '[redacted].

xi. Respiratory - Delete [redacted].

xii. Add the following as the last subsection in this section:

Postmarketing Experience
Postmarketing experience with butorphanol tartrate nasal spray has shown an adverse event profile similar to that seen during the premarketing evaluation of butorphanol by all routes of administration. Adverse experiences that were associated with the use of butorphanol tartrate nasal spray or butorphanol tartrate injection and that are not listed above have been chosen for inclusion below because of their seriousness, frequency of reporting, or probable relationship to butorphanol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These adverse experiences include apnea, convulsion, delusion, drug dependence, excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements, overdose, and vertigo. Reports of butorphanol overdose with a fatal outcome have usually but not always been associated with ingestion of multiple drugs.

h. DRUG ABUSE AND DEPENDENCE

Revise this section as follows:

Butorphanol tartrate nasal spray is listed in Schedule IV of the Controlled Substances Act (CSA).

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 continuous basis for an extended period.

Clinical Trial Experience
In all clinical trials, less than 1% of patients using butorphanol tartrate nasal spray had experiences that

suggested the development of physical dependence or tolerance. Much of this information is based on experience with patients who did not have prolonged continuous exposure to butorphanol tartrate nasal spray. However, in one controlled clinical trial where patients with chronic pain from nonmalignant disease were treated with butorphanol tartrate nasal spray (n=303) or placebo (n=99) for up to 6 months, overuse (which may suggest the development of tolerance) was reported in nine (2.9%) patients receiving butorphanol tartrate nasal spray and no patients receiving placebo. Probable withdrawal symptoms were reported in eight (2.6%) patients using butorphanol tartrate nasal spray and no patients receiving placebo in the chronic nonmalignant pain study. Most of these patients abruptly discontinued butorphanol tartrate nasal spray after extended use or high doses. Symptoms suggestive of withdrawal included anxiety, agitation, tremulousness, diarrhea, chills, sweats, insomnia, confusion, incoordination, 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.

i. OVERDOSAGE

i. First paragraph - ... of butorphanol overdose ... of opioid drugs in general. Consequences of overdose vary with the amount of butorphanol ingested and individual response to the effects of opiates. The most serious symptoms are ... insufficiency, coma, and death. Butorphanol overdose may be associated with ingestion of multiple drugs (see **ADVERSE REACTIONS: Postmarketing Experience** section).

ii. "Treatment" is a subsection of the "OVERDOSAGE" section and the heading should have the same prominence as "Clinical Manifestations".

iii. Add the following as the last paragraph:

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

j. DOSAGE AND ADMINISTRATION

i. Decrease the prominence of the subsection headings.

ii. First paragraph, second sentence - ... CLINICAL PHARMACOLOGY, Individualization of Dosage).

iii. Use for Pain, second paragraph - The initial dose ... 3 to 4 hours as required after the second dose of the sequence.

iv. Use in Balanced Anesthesia - ... butorphanol tartrate nasal spray is ...

v. Labor - Delete the first paragraph.

vi. Safety and Handling - Add the following as the first sentence of the last paragraph:

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

k. HOW SUPPLIED

i. Storage Conditions - Store below 25°C (77°F).

ii. Please include the full text of the MEDICATION GUIDE and the Patient Instructions at the end of the insert.

Please revise your container labels and insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachments: Innovator approval letter and MEDICATION GUIDE

Copy of Reference Listed Drug labeling removed.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

December 3, 1999

Office of Generic Drugs
CDER, FDA
MPNII, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

Notice of Litigation
Novex/Apotex sued w/in
45 days.
12/16/99

PATENT AMENDMENT

Re: ANDA 75-499
Butorphanol Tartrate Nasal Spray
10 mg/mL

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a division of Apotex, Inc. of Ontario, Canada, hereby submits Notice of Litigation pursuant to the accepted for filing letter dated February 2, 1999.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

ANDA 75-499

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

MAY 16 2000

Dear Madam:

This letter is in reference to your Abbreviated New Drug Application (ANDA) dated November 4, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 1 mg/spray.

We refer you to our "Not Approvable" letter dated September 9, 1999, which detailed the deficiencies identified during our review of your ANDA. The Agency may consider an ANDA applicant's failure to respond to a "Not Approvable" letter within 180 days to be a request by the applicant to withdraw the ANDA under 314.120(b). Your amendment to the application is overdue. You must amend your application within 10 days of receipt of this letter. Otherwise, an action to withdraw the application will be initiated per 21 CFR 314.99.

If you do not wish to pursue approval of this application at this time, you should request withdrawal in accord with 21 CFR 314.65. A decision to withdraw the application would be without prejudice to refiling.

Please send all correspondence to the following address:

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

Sincerely yours,

Harvey A. Strongin
for

Wm Peter Rickmam
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 75-499
DUP/Division File
HFD-610/PRickman

Endorsement:
HFD-617/NMahmud, Chief, RSB, H Thaeby date 5/4/00
HFD-617/SMiddleton, CSO, S. Middleton date 5/5/00
Word File
V:\FIRMSNZ\NOVEX\LTRS&REV\75499.OTH
F/T by mjl\5\3\00
10 DAY LETTER!

APPEARS THIS WAY
ON ORIGINAL

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

June 5, 2000

NEW CORRESP
NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

RESPONSE TO "NOT APPROVABLE" LETTER

RE: ANDA 75-499
Butorphanol Tartrate Nasal Spray 10 mg/mL

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding in duplicate a response to the "Not Approvable" letter dated September 9, 1999.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

KK

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG
REC'D
JUN 07 2000
OGD
EVALUATION AND RESEARCH

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

June 01, 2000

Mr. Wm. Peter Rickman, Acting Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER, FDA
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD U.S.A. 20855-2773

Dear Mr. Rickman:

RE: RESPONSE TO "NOT APPROVABLE" LETTER
Butorphanol Tartrate Nasal Spray 10 mg/mL, ANDA # 75-499

This response is in regard to your letter dated May 16, 2000 where you reference your "Not Approvable" letter dated September 09, 1999 indicating Novex Pharma's failure to respond within the 180-day limit.

We would like to apologize for our delayed response to your Major Amendment letter. During the preparation of our response, we were advised by the supplier of one of our packaging components (the metering nasal pump) that they have made a change to one of the materials used as part of the component. Therefore, in order to notify FDA of the above, we have since been gathering the appropriate supportive documentation and data regarding the change for incorporation into our response to your "Not Approvable" letter.

Therefore, we would ask that you do not withdraw this application for Butorphanol Tartrate Nasal Spray 10 mg/mL as per CFR 314.99, as our response to the Major Amendment is close to completion and will be forwarded to you by July, 2000.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Manager, Regulatory Affairs

DC:cl

File

ANDA 75-499

Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hill, IL 60061

JUN 7 2000

Dear Madam:

Please refer to your Abbreviated New Drug Application dated November 4, 1998, submitted pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 1 mg/spray.

Reference is also made to the certified letter sent to you on May 16, 2000. We are unaware of any subsequent correspondence from you since our letter.

Therefore, in accordance with Section 314.65 of the regulations under the Federal Food, Drug and Cosmetic Act, the application is regarded as withdrawn. This withdrawal does not prejudice any future filing of the application. You may request that the information in this application be considered in connection with any resubmission.

Sincerely yours,

Sandra J. Middleton
for Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-499
HFD-600/Division File
HFD-320/JFamulare
HFD-615/NMahmud
HFD-613/labeling **only for labeling supplemental**
Endorsements:
for
HFD-615 NMahmud, Chief S. Middleton date 6/7/00
HFD-615 SMiddleton, CSO S. Middleton date 6/7/00
Word Document
V:\FIRMSNZ\NOVEX\LTRS&REV\75499WDAD.UNA
FT\StM 6/7/00
Administrative Withdrawal of Unapproved Application!

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

June ~~28~~ 29, 2000

NDA ORIG AMENDMENT

N/AC

FPL

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

MAJOR AMENDMENT

RE: ANDA 75-499
Butorphanol Tartrate Nasal Spray 10 mg/mL

To Whom It May Concern:

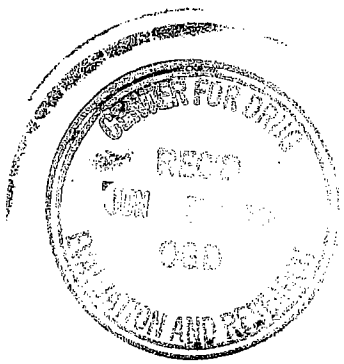
Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding a major amendment in duplicate in response to the deficiency letter dated September 09, 1999.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223



APOTEX CORP.

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August 21, 2000

BIOAVAILABILITY

AMENDMENT

N/AB

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

BIOEQUIVALENCY AMENDMENT

RE: ANDA 75-499
Butorphanol Tartrate Nasal Spray 10 mg/mL

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding a bioequivalency amendment in duplicate in response to the deficiency letter dated June 07, 1999.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 23 2000
OGD

3.1

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

ORIG AMENDMENT

N/A

August 22, 2000

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

MINOR AMENDMENT

RE: ANDA 75-499
Butorphanol Tartrate Nasal Spray 10 mg/mL

To Whom It May Concern:

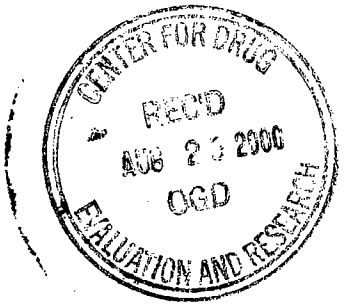
Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding a minor amendment in duplicate. A field copy is also enclosed.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223



APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

October 19, 2000

NEW CORRESP

NC / bio

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

BIOEQUIVALENCY
TELEPHONE AMENDMENT

RE: Butorphanol Tartrate Nasal Spray 10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding the response to a bioequivalency telephone amendment in duplicate.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 24 2000
OGD

APOTEX CORP.

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October 31, 2000

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC/Bio

BIOEQUIVALENCY
TELEPHONE AMENDMENT

RE: Butorphanol Tartrate Nasal Spray 10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding the response to a bioequivalency telephone amendment in duplicate.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Mary Macdonald

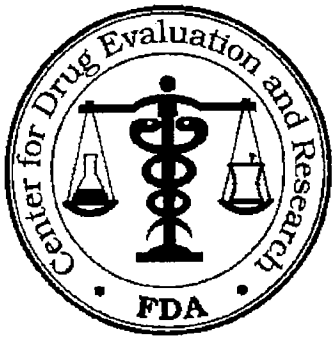
Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

MAJOR AMENDMENT

ANDA 75-499

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

DEC 22 [illegible]



TO: APPLICANT: Novex Pharma — TEL: 847-573-9999

ATTN: Marcy Macdonald — FAX: 847-573-1001

FROM: Jeen Min — PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 4, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 10 mg/mL.

Reference is also made to your amendment(s) dated: June 29 and August 22, 2000.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (6 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance

SPECIAL INSTRUCTIONS:

Chemistry and Labeling comments.

JM 12/21/00

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

12/22/2000 FDA FAX

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

ANDA Number: **75-499** Date of Submission: **June 29, 2000**

Applicant's Name: **Novex Pharma**

Established Name: **Butorphanol Tartrate Nasal Spray, 1 mg/spray**
10 mg/mL (2.5 mL)

Labeling Deficiencies:

1. CARTON

   We note that you have not submitted carton labeling for your drug product. Please submit and/or comment.

2. PATIENT INSTRUCTIONS

   a. We note you have submitted computer-generated printer's proof as your final printed Patient Instructions Leaflet. Although we will accept printer's proof for container labels and carton labeling, you must submit final printed Patient Instructions Leaflet prior to the approval of this application.

   b. First "NOTE" – "1" rather than "I"

3. MEDICATION GUIDE

   a. See comment above under (a) PATIENT INSTRUCTIONS

   b. Although we believe that the printing size of Medication Guide (printed along with Patient Instructions) meets the minimum requirement, it is rather difficult to read your labeling due to the poor quality of printing. We strongly encourage you to increase the readability of your Medication Guide.

   c. Boxed Statements – First item, second sentence:

      ...nasal spray belongs to a group of... [delete ———————]

   d. Who should not take butorphanol tartrate nasal spray? – Third sentence:

      Butorphanol tartrate has been found... [delete ———————]

   e. What should I avoid while taking butorphanol tartrate nasal spray? – Penultimate bullet:

      Delete ———————

4. INSERT

   a. You may delete the terms "PRESCRIBING INFORMATION" if you adopt to do so.

   b. DESCRIPTION

      i. Molecular formula – Add a comma between "O_2" and "C_4".

      ii. Revise the molecular weight to read "477.55".

c. CLINICAL PHARMACOLOGY

i. General Pharmacology and Mechanism of Action – First paragraph:

... an antagonist at k-opioid receptors. ["k" should appear with proper prominence]

ii. Clinical Trials (Use in the Management of Pain, Migraine Headache Pain) – Last sentence:

... with the 1 mg... [add "the"]

d. PRECAUTIONS (Labor and Delivery)

Upon further review we ask that you delete the first two paragraphs, which are specifically associated with injection form of butorphanol tartrate.

e. HOW SUPPLIED

We encourage the relocation of the storage requirement statement so that it appears in this section, not in the Medication Guide.

Please revise your labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

Adolph Vezza for/

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

April 18, 2001

NEW CORRESP
NC

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

Emily Thomas
4/23/01
NAI

REVISED PATENT CERTIFICATION

RE: ANDA 75-499
Butorphanol Tartrate Nasal Spray
10 mg/mL

To Whom It May Concern:

As the U.S. agent for Novex Pharma, a Division of Apotex, Inc., of Ontario, Canada, is hereby forwarding in duplicate a copy of the original Paragraph IV Patent Certification is being revised to Paragraph Certification III.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald /HF

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND ... RECD APR 20 2001 OGD

PIV changed to PIII
NAI 5/7/01

BIOEQUIVALENCY AMENDMENT

ANDA 75-499

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APR 30 2001

TO: APPLICANT: Novex Pharma

TEL: 905-508-2562

ATTN: Marcy Macdonald

FAX: 905-884-0357

FROM: Steven Mazzella

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on August 22, 21 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray.

Reference is also made to your amendment(s) dated: June 29, 2000, October 31, 2000, and January 15, 2001.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

4.1
Memo

BIOEQUIVALENCY DEFICIENCIES APR 30 2001

ANDA: 75-499 APPLICANT: Novex Pharma

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Based on the droplet size distribution plots for individual sprays (percent transmission vs. time along with D10, D50, D90) submitted on 11 January 2001, the data supporting droplet size distribution by laser diffraction are unacceptable. This is because aberrant, and apparently random, spikes occur in the D50 data in the intermediate (fully formed plume) phase of the spray. These spikes represent up to approximately 3 times the magnitude of most D50 values in the same plot. These spikes were observed at all distances, and represent excessive and unacceptable variability during the most stable portion of the plume. This is much greater variability than has been observed in laser diffraction analyses, hitherto.

The variability may be due to your performance of the method or may be a characteristic of your product. Please investigate your method to determine if it is being applied appropriately. For example, the aberrant spikes may occur due to reentry of large droplets into the path of the laser beam as a result of inadequate airflow. The influence of airflow rate on the variability of D50 should be investigated during method validation. After correcting the problem, please provide complete droplet size distribution data. The repeat test should be performed using the same three lots of the test and reference products, if these batches are still within the expiry date.

For each spray, please provide D10, D50, D90 and Span data for the following stages of plume life based on % obscurations (or transmission) of the laser beam:

A. Plume formation characterized by increase in % obscuration or decrease in % transmission.

B. Fully formed plume characterized by a period of relatively stable obscuration/transmission.

C. Dissipating plume characterized by decrease in obscuration or increase in transmission relative to B.

Please provide a revised SOP and representative (≥ 20%) plots of obscuration/transmission vs. time (msec) with the revised droplet size distribution data. These graphs should also contain plots of D10, D50 and D90 vs. time data. Please also submit, if possible, data regarding the duration of "fully formed plume" of test and reference products.

2. The plume angles were measured at a delay time of 2 msec which represents the very initial phase of plume formation rather than the fully formed plume. Plume angle at later times was not reported. Therefore, plume angle data you submitted does not represent angle of the fully formed plume. Please provide plume angle data at later delay times. The plume angle data should include one angle measurement during plume formation when the plume is still in contact with actuator (e.g., at time delays of 10-50 msec).

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

May 23, 2001

Mr. Jeen Min, Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
NIAC

Dear Mr. Min:

Re: MAJOR AMENDMENT
Butorphanol Tartrate Nasal Spray 10 mg/mL, ANDA #75-499

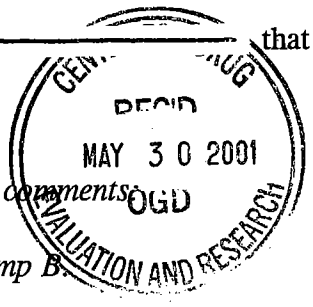
Further to your Major Amendment letter dated December 22, 2000, we are pleased to provide you with our responses in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2. A signed Field Copy Certification has been included as Attachment No. 3.

Please note: We have noticed that in your deficiency letter there were 2 sets of CMC questions identified as #3 (i.e., 3a-h followed by 3a-c). Therefore, for ease of identification, we have re-labeled questions 3a-c as 4a-c throughout this amendment.

DEFICIENCIES:

1. *DMF #——is deficient. The DMF holder will be informed of the deficiencies.*

   Response: We have been advised by——————————that they responded to the DMF deficiencies on February 23, 2001.



2. *Regarding the proposed new Pump B, we have the following comments:*

   a. *Please provide Manufacturer's and in-house CoA for Pump B.*

      Response: As requested, an in-house certificate of analysis has been provided for review in Attachment No. 4 of this amendment, along with the corresponding IR spectra of the various pump components. However, we are not able to provide a manufacturer's

.../cont'd

Redacted 9 page(s)

of trade secret and/or

confidential commercial

information from

5/23/2001 NOVEX LETTER

LABELING DEFICIENCIES:

1. *CARTON*
   We note that you have not submitted carton labeling for your drug product. Please submit and/or comment.

   Response: Similar to the packaging format used by the innovator, we have proposed to use a child-resistant, clear plastic vial as the outer container for the bottle, spray pump and insert labeling. Therefore, the information usually required for a carton will be included on a flat label to be adhered to the plastic cylinder. Copies of the printer's proofs for this label can be found in Attachment No. 22, along with the other labeling components.

2. *PATIENT INSTRUCTIONS*
   a. *We note you have submitted computer-generated printer's proof as your final printed Patient Instructions Leaflet. Although we will accept printer's proof for container labels and carton labeling, you must submit final printed Patient Instructions Leaflet prior to the approval of this application.*

   b. *First "NOTE" - "1" rather than "I"*

   Response: As requested, the Patient Instructions have been revised as instructed above, and copies of the printer's proofs have been submitted in Attachment No. 22 of this amendment.

   Please note that since our last amendment, we have revised the format and layout of our Patient Instructions, Medication Guide and Prescribing Information insert. Rather than using an expanded content label for the patient information, we have included both the patient information and professional information in a single insert with a perforation to allow the pharmacist to remove the Medication Guide and Patient Instructions and dispense to the patient.

3. *MEDICATION GUIDE*
   a. *See comment above under (a) PATIENT INSTRUCTIONS*

   b. *Although we believe that the printing size of Medication Guide (printed along with Patient Instructions) meets the minimum requirement, it is rather difficult to read your labeling due to the poor quality of printing. We strongly encourage you to increase the readability of your Medication Guide.*

   c. *Boxed Statements - First item, second sentence:*
   ...nasal spray belongs to a group of... [delete " ——————— *"*

   d. *Who should not take butorphanol tartrate nasal spray? - Third sentence:*
   Butorphanol tartrate has been found... [delete " ———— *"*

.../cont'd

e. *What should I avoid while taking butorphanol tartrate nasal spray? - Penultimate bullet: Delete* ———

Response: As requested, the Medication Guide has been revised as instructed above. Please see our response to Labeling Deficiency 2 above for a description of revisions we have made to our labeling format.

4. *INSERT*
   a. *You may delete the terms "PRESCRIBING INFORMATION" if you adopt to do so.*

   b. *DESCRIPTION*
      i. *Molecular formula - Add a comma between "O_2" and "C_4".*
      ii. *Revise the molecular weight to read "477.55".*

   c. *CLINICAL PHARMACOLOGY*
      i. *General Pharmacology and Mechanism of Action - First paragraph:*
      ... an antagonist at k-opioid receptors. ["k" should appear with proper prominence]
      ii. *Clinical Trials (Use in the Management of Pain. Migraine Headache Pain) - Last sentence:*
      ... with the 1 mg... [add "the"]

   d. *PRECAUTIONS (Labor and Delivery)*
   Upon further review we ask that you delete the first two paragraphs, which are specifically associated with injection form of butorphanol tartrate.

   e. *HOW SUPPLIED*
   We encourage the relocation of the storage requirement statement so that it appears in this section, not in the Medication Guide.

Please revise your labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Response: As requested, we have revised the insert labeling as instructed above, except that we have chosen to retain the "PRESCRIBING INFORMATION" heading for internal documentation purposes. In addition, please see our response to Labeling Deficiency 2 above for a description of revisions we have made to our labeling format.

As requested, we have provided twelve (12) copies of the printer's proofs for the bottle and cylinder labels in Attachment No. 22 of this amendment. We hereby confirm that the

.../cont'd

printer's proofs are a true representation of the final printed labeling and trust that they will be acceptable for approval of this application.

For the insert labeling (including the Patient Instructions, Medication Guide and Prescribing Information), we have provided four (4) copies of the printer's proofs for a tentative approval (also in Attachment No. 22). We will submit twelve (12) copies of the final printed insert for a full approval as soon as they become available.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes.
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

Response: As requested, and in accordance with 21 CFR 314.94(a)(8)(iv), we have provided side-by-side comparisons of our proposed labeling with our last submission, with all differences annotated and explained, in Attachment No. 21 of this amendment.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Manager, Regulatory Affairs

DC:mt

Encl.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

May 25, 2001

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N1 AC

MAJOR AMENDMENT

RE: Butorphanol Tartrate Nasal Spray 10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, of Ontario, Canada, is hereby forwarding the response to a major amendment in duplicate. A Field Copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Apotex

ATTN: Marcy McDonald (US Agent for Novex)

TEL: 847-573-9999 X223

FAX: 847-573-1001

PROJECT MANAGER: 301-594-0338

FROM: Jeen Min

Number of pages: 14
(excluding the cover sheet)

Comments:

Labeling deficiencies for ANDA 75-499 (Butorphanol Tartrate Nasal Spray).

Jen 11/2/01

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

ANDA Number: **75-499** Date of Submission: **May 25, 2001**

Applicant's Name: **Novex Pharma**

Established Name: **Butorphanol Tartrate Nasal Spray, 1 mg/spray**
10 mg/mL (2.5 mL)

Labeling Deficiencies:

1. GENERAL

   Upon further review, we ask that you revise the storage temperature requirement to read "Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F) [see USP]".

2. CONTAINER

   a. See general comment above.

   b. Revise the text '[redacted]' to read "Usual Dosage: Read enclosed circular for dosage information and patient instructions.".

   c. Please assure that your packaging system meets the requirement found in 21 CFR 1302.06. Please include information on your provision in your next chemistry amendment.

3. CARTON

   a. See general comment above.

   b. Please include the net quantity statement. We suggest the following:

      2.5 mL Bottle and Spray Pump

   c. Boxed statement "Pharmacy label... dispensing.".

      i. Please assure that you allow enough space for the pharmacy label.

      ii. Add the following text as the last sentence in a prominent manner:

         Dispense with patient instructions and medication guide.

4. PATIENT INSTRUCTIONS

   Please assure that your patient instruction can be easily detached (*i.e.*, perforated) from the professional package insert.

5. MEDICATION GUIDE

   See comment above under PATIENT INSTRUCTIONS.

6. INSERT

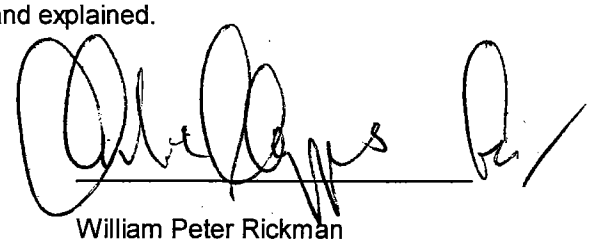
   a. See general comment above.

b. The insert labeling for the reference listed drug has been recently revised and approved on January 5, 2001. Please revise your insert labeling to be in accordance with the attached Stadol NS® insert labeling. We remind you that you must not include information regarding the use of your drug product during "labor" as that indication is restricted to the injection.

Please revise your labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.



William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: A copy of the Stadol NS® package insert labeling

Copy of Reference Listed Drug labeling removed.

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2060
Facsimile 905 884-9876

November 14, 2001

Mr. Jeen Min, Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Min:

Re: TELEPHONE AMENDMENT
Butorphanol Tartrate Nasal Spray 10 mg/mL, ANDA No. 75-499

Further to your telephone request on November 05, 2001, we are pleased to provide you with our response in triplicate (Archival, Review and Field copies). For ease of review, this amendment has been prepared in a request-and-response format. An Application Form FDA 356h can be found in Attachment No. 1 of this amendment, and a Field Copy Certification is provided as Attachment No. 2.

1) *For method TM-767:*
   a) *Include a range for the RRT of the known impurity.*
   b) *For System Suitability, include a specific range for butorphanol tartrate retention time.*

Response: Test Method No. TM-767 has been revised as requested and has been included for review in Attachment No. 3 of this amendment.

2) *Revise the shelf-life stability protocol to indicate that analyses on the first three post-approval validation batches will be conducted using three separate lots of the spray pumps (i.e., a different lot of spray pumps for each validation batch).*

Response: The shelf-life stability protocol has been revised as requested and has been included for review in Attachment No. 4 of this amendment.

.../cont'd

3) *Explain how the expiration date is calculated (i.e., 24 months from what time point?).*

Response: The expiration date is calculated as 24 months from the date of manufacture. The date of manufacture is defined as the date upon which the active ingredient is added to the formulation as per the Manufacturing Instructions.

4) *Please commit to perform priming and re-priming studies based on spray content uniformity on one post-approval batch using three separate lots of spray pumps. The samples should be in the horizontal position, and should be analyzed for two different periods of non-use.*

Response: Novex Pharma hereby commits to perform priming and re-priming studies, based on spray content uniformity, on one post-approval batch of Butorphanol Tartrate Nasal Spray using three separate lots of nasal spray pumps. The samples will be stored in the horizontal position and will be analyzed for two different periods of non-use.

5) *Provide a statement of conformance to 21 CFR 1302.06 for the packaging system.*

Response: Novex Pharma hereby confirms that the packaging system for Butorphanol Tartrate Nasal Spray conforms to 21 CFR 1302.06.

The above requirement is met by use of a tamper-evident induction-seal on the plastic cylinder which contains the 2.5 mL bottle of nasal spray, the spray pump and the package insert.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Manager, Regulatory Affairs

DC:kf

Encl.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

N/AF

November 16, 2001

ORIG AMENDMENT

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

LABELING AMENDMENT

RE: Butorphanol Tartrate Nasal Spray 10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, of Ontario, Canada, is hereby forwarding in dupilcate the response to a labeling amendment in response to FDA dated May 23, 2001 and further to major amendment letter dated December 22, 2000.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Fax 847-573-1001

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

November 16, 2001

N/AC

ORIG AMENDMENT

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

TELEPHONE AMENDMENT

RE: Butorphanol Tartrate Nasal Spray 10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, of Ontario, Canada, is hereby forwarding in duplicate a telephone amendment in response to telephone request on November 05, 2001. A Field Copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald JB

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 28 2001

MINOR AMENDMENT

ANDA 75-499

NOV 2 9

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Apotex Corp. TEL: 847-573-9999 X223

ATTN: Marcy MacDonald (US Agent for Novex) FAX: 847-573-1001

FROM: Jeen Min PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 10 mg/mL.

Reference is also made to your amendment(s) dated: June 29, August 21 & 22, and October 31, 2000; January 15 and May 25, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

jm 11/29/01

38. Chemistry Comments to be Provided to the Applicant

ANDA 75-499 Applicant Novex Pharma

Drug Product Butorphanol Tartrate Nasal Spray

The deficiency presented below represent a Minor deficiency.

The Division of Chemistry has no further questions at this time. We refer to the facsimile dated April 30, 2001 regarding deficiencies in the bioequivalency section of your application. These deficiencies must be answered satisfactorily before the application can be approved. Please note that any changes made to the chemistry, manufacturing and controls section of your application as a result of outstanding bioequivalency deficiencies must be submitted and could result in the response being considered a MAJOR Amendment.

Sincerely yours,

for Nayat Sayed

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

November 29, 2001

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

N/A B

BIOEQUIVALENCY AMENDMENT

RE: Butorphanol Tartrate Nasal Spray
10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, of Ontario, Canada, is hereby forwarding in duplicate a bioequivalency amendment in response to the FDA Bioequivalency deficiency letter dated April 30, 2001.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

ORIG AMENDMENT
N/ANA.

December 3, 2001

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

MINOR AMENDMENT

RE: Butorphanol Tartrate Nasal Spray 10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, of Ontario, Canada, is hereby forwarding in duplicate a minor amendment in response to FDA letter dated November 29, 2001. A Field Copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald /NS

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 10 2001

12/20/01

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

ORIG AMENDMENT
N/AF

January 18, 2002

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

LABELING AMENDMENT

RE: Butorphanol Tartrate Nasal Spray 10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, of Ontario, Canada, is hereby forwarding in duplicate a labeling amendment in response to FDA letter dated December 11, 2001.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG
JAN 25 2002
EVALUATION AND RESEARCH

847-573-1001
(fax)

********** -COMM. JOURNAL- ********** DATE FEB-07-2002 ***** TIME 15:47 *********

MODE = MEMORY TRANSMISSION START=FEB-07 15:46 END=FEB-07 15:47

FILE NO.=001

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
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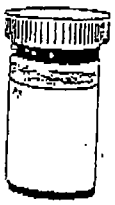
-FDA CDER OGD LPS -

********** - ***** - **********

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: Feb 7, 02

To: Marcy Macdonald

Phone: 847-573-9999 Fax: 847-573-1001

From: Chan Park 21.223

Phone: (301) 827-5846 Fax: (301) 443-3847

Number of Pages: 3
(Including Cover Sheet)

Comments: ANDA 75-499
Labeling deficiency per Tele-Con. Thanks,
Chan

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

ANDA Number: **75- 499** Date of Submission: **November 16, & January 18, 2002**

Applicant's Name: **Novex Pharma**

Established Name: **Butorphanol Tartrate Nasal Spray, 1 mg/spray**
10 mg/mL (2.5 mL)

Labeling Deficiencies:

1. CONTAINER

   a. We note that you have submitted only one copy of FPL in this submission. You are required to submit 12 copies. We refer you to 21 CFR 314.94(a)(8)(ii) for guidance.

   b. Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please assure that these criteria are met prior to submission of final print.

2. CARTON

   See comments under CONTAINER.

3. INSERT

   a. GENERAL

      i. As addressed in the Tele-conference between Marcy Macdonald of your firm and Chan Park of the Agency on January 28 and January 30, 2002, the following comment is based on the last approved labeling for Stadol® Nasal Spray (approved on January 14, 2002).

      ii. See comment (a) under CONTAINER.

   b. PRECAUTIONS (Drug Interactions)

      i. Revise the second paragraph to read as follows:

      ... a single 6 mg subcutaneous dose of sumatriptan. However, in another study in healthy volunteers, the pharmacokinetics of butorphanol were significantly altered (29% decrease in AUC and 38% decrease in C_{max}) when a 1 mg dose of butorphanol tartrate nasal spray was administered 1 minute after a 20 mg dose of sumatriptan nasal spray. (The two drugs were administered in opposite nostrils.) When the butorphanol tartrate nasal spray was administered 30 minutes after the sumatriptan nasal spray, the AUC of butorphanol increased 11% and C_{max} decreased 18%. In neither case was the pharmacokinetics of sumatriptan affected by co-administration with butorphanol tartrate nasal spray. These results suggest that the analgesic effect of butorphanol tartrate nasal spray may be diminished when it is administered shortly after sumatriptan nasal spray, but by 30 minutes any such reduction in effect should be minimal.

ii. Include the following text as the new third paragraph:

The safety of using butorphanol tartrate nasal spray and Imitrex® (sumatriptan) nasal spray during the same episode of migraine has not been established. However, it should be noted that both products are capable of producing transient increases in blood pressure.

[Please include a disclaimer stating that Imitrex® is the registered trademark of Glaxo Wellcome, Inc.]

Please revise your labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY AMENDMENT

ANDA 75-499

MAR - 1 2002

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

847-573-9999

TO: APPLICANT: Novex Pharma

TEL: ~~905-508-2562~~

ATTN: Marcy Macdonald

FAX: ~~905-884-0357~~ 847-573-1001

FROM: Steven Mazzella

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 29, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 10 mg/mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

sm

MAR - 1 2002

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-499 APPLICANT: Novex Pharma

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Evaluation of equivalence of D50 and SPAN data is based on the intermediate portion of the test and reference product sprays, as it represents the stable portion of the plume. For the middle sector of the product life, the test/reference geometric mean ratios for D50 are outside the 0.90-1.11 range, used by the Division of Bioequivalence for acceptance of D50 data for nasal spray products. For the middle sector, the test failed to meet the 0.9-1.11 range at all three distances (3, 5 and 8 cm). Therefore, the test product D50 is not equivalent to the reference product D50.

In response to the Agency's request, you submitted the spray plume duration data. Though such data are not evaluated to determine product equivalence, your data were analyzed to determine similarity in spray plume duration, in light of the above deficiency. Based on the Agency analysis, the duration of the intermediate portion of the test product plume is different from that of the reference product. At the beginning and end sectors, the test product's spray plume duration is within 89-95% of that the reference product, and for most comparisons the observed differences are not statistically significant ($p > 0.05$). On the other hand, for the middle sector, the duration of the intermediate portion of the test product plume is 17-21% shorter than that of the reference product, and the observed differences are highly significant ($p<0.0001$)

These data indicate that, at the middle sector, the intermediate portions of the spray plumes of the test and reference products were maintained for significantly different durations. The Agency is uncertain regarding the impact of the observed difference in duration of the intermediate portion of the test and reference spray plumes upon D50 values. This may be a contributing factor to the

observed difference in the test and reference product D50 values at the middle sector.

Due to lack of equivalence of the test and reference product with regard to droplet size distribution, your application remains incomplete from the bioequivalence viewpoint. You may repeat the laser diffraction analysis and submit the revised data to support equivalence of droplet size distribution. The revised data should be accompanied by the SOP used and representative (≥ 20%) plots of obscuration/transmission vs. time (msec).

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

March 6, 2002

N/AF
ORIG AMENDMENT

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

LABELING AMENDMENT

RE: Butorphanol Tartrate Nasal Spray
10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, of Ontario, Canada, is hereby forwarding a labeling amendment in duplicate in response to the FDA label deficiency letter dated February 07, 2002.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

RECEIVED
MAR 13 2002
OGD / CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

April 04, 2002

Mr. Steven Mazzella
Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A 0

Dear Mr. Mazzella:

Re: BIOEQUIVALENCY AMENDMENT
Butorphanol Tartrate Nasal Spray 10 mg/mL, ANDA No. 75-499

Further to your Bioequivalency Amendment letter dated March 01, 2002, we are pleased to provide you with our responses in duplicate. For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

BIOEQUIVALENCY DEFICIENCIES

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Evaluation of equivalence of D50 and SPAN data is based on the intermediate portion of the test and reference product sprays, as it represents the stable portion of the plume. For the middle sector of the product life, the test/reference geometric mean ratios for D50 are outside the 0.90-1.11 range, used by the Division of Bioequivalence for acceptance of D50 data for nasal spray products. For the middle sector, the test failed to meet the 0.9-1.11 range at all three distances (3, 5 and 8 cm). Therefore, the test product D50 is not equivalent to the reference product D50.

In response to the Agency's request, you submitted the spray plume duration data. Though such data are not evaluated to determine product equivalence, your data were analyzed to determine similarity in spray plume duration, in light of the above deficiency. Based on

.../cont'd

the Agency analysis, the duration of the intermediate portion of the test product plume is different from that of the reference product. At the beginning and end sectors, the test product's spray plume duration is within 89-95% of that of the reference product, and for most comparisons the observed differences are not statistically significant ($p > 0.05$). On the other hand, for the middle sector, the duration of the intermediate portion of the test product plume is 17-21% shorter than that of the reference product, and the observed differences are highly significant ($p < 0.0001$).

These data indicate that, at the middle sector, the intermediate portions of the spray plumes of the test and reference products were maintained for significantly different durations. The Agency is uncertain regarding the impact of the observed difference in duration of the intermediate portion of the test and reference spray plumes upon D50 values. This may be a contributing factor to the observed difference in the test and reference product D50 values at the middle sector.

Due to lack of equivalence of the test and reference product with regard to droplet size distribution, your application remains incomplete from the bioequivalence viewpoint. You may repeat the laser diffraction analysis and submit the revised data to support equivalence of droplet size distribution. The revised data should be accompanied by the SOP used and representative (≥20%) plots of obscuration/transmission vs. time (msec).

Response: In response to the above-noted deficiency, we have reviewed the collection of the previously submitted D_{50} droplet size distribution data, and noticed that the data at the middle sector of the product life were obtained after a period of non-use (overnight). The Novex Pharma product requires only one (1) spray to reprime, as demonstrated by the previously submitted repriming data. For this reason, and to conserve product sprays for other analyses, only one spray was used to reprime both the test and reference listed drug (RLD) products. However, upon further evaluation of the repriming data submitted for the RLD, we realized that the RLD requires two (2) sprays to reprime. We felt that this may be a factor contributing to the observed differences in D_{50} values and spray duration. Therefore, we have repeated the droplet size distribution data acquisition without interruption, and have provided the individual data in tabular format, followed by a comparative summary table of the test and reference product data at various distances to the laser beam. Also tabulated are the ratio of mean D values between the test and reference products to demonstrate that the droplet size of the Novex product is within the 0.90 - 1.10 range. These data summaries have been enclosed for your review in Attachment No. 3 of this amendment. In addition, we have enclosed the spray duration data corresponding to this analysis, for your information, in Attachment No. 4. An electronic (diskette) copy of the data summaries can be found in Attachment No. 3.

As requested, representative (20%) obscuration/transmission vs. time plots are included in Attachment No. 5. In addition, a copy of the test methods used (GM-155 and GM-143)

.../cont'd

can be found as Attachment No. 6 (refer to the pump specific parameters for the —— pump in Table Nos. 1 and 2 of GM-143).

Please note that we did not have sufficient quantities from three lots of the RLD to complete the required repeat testing, therefore, we have used five bottles from each of Lot Nos. 0J30529 and 0H29692, ten (10) bottles from Lot No. 9F5910, four (4) bottles from Lot No. 0L31505 and six (6) bottles from Lot No. M8K050B, for a total of 30 bottles of the RLD.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 884-2050, or FAX your requests to (905) 884-0357.

Yours sincerely,

for: Dawn Culp, B.Sc.
Manager, Regulatory Affairs

DC:kf

Encl.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

April 29, 2002

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

BIOEQUIVALENCY TELEPHONE AMENDMENT

NEW CORRESP
NC

RE: Butorphanol Tartrate Nasal Spray
10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, of Ontario, Canada, is hereby forwarding in duplicate a bioequivalency telephone amendment in response to the FDA Bioequivalency deficiency letter dated April 25, 2002.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

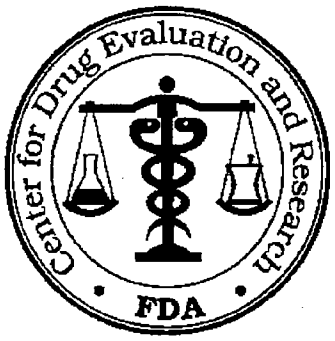
RECEIVED
MAY 0 7 2002
OGD / CDER

BIOEQUIVALENCY AMENDMENT

ANDA 75-499

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAY - 9 2002



TO: APPLICANT: Novex Pharma

TEL: 905-508-2562

ATTN: Marcy Macdonald

FAX: 905-884-0357

FROM: Steven Mazzella

PROJECT MANAGER: 301-827-5847

Dear Ms Macdonald:

This facsimile is in reference to the bioequivalency data submitted on April 5, 2002 and ~~April 26, 2002,~~ April 29, 2002 (KS) pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 10 mg/mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MAY - 9 2002

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-499 APPLICANT: Novex Pharma

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

You used two expired lots of the reference product (lot #M8K050B, EXP. December/2000 and lot #9F5910, EXP. June/2001) at the time of Droplet Size Distribution testing (3/2002). Therefore, the testing results for D50 and SPAN are invalid.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

ANDA 75-499

MAY 20 2002

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Apotex Corp.

ATTN: Marcy MacDonald
(US Agent for Novex Pharma)

TEL: 847-573-9999

FAX: 847-573-1001

PROJECT MANAGER: 301-827-5849

FROM: Jeen Min

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 4, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 10 mg/mL (1 mg/spray).

Reference is also made to your amendment(s) dated: June 29, 2000; November 16 and December 3, 2001; January 18 and March 6, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

jm 5/20/02

MAY 20 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA 75-499 Applicant: Novex Pharma

Drug Product: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The deficiencies presented below represent MINOR deficiencies.

The Division of Chemistry has no further questions at this time. We refer to the facsimile dated, May 9, 2002 regarding deficiencies in the bioequivalence section of your application. These deficiencies must be answered satisfactorily before the application can be approved. Please note that any changes made to the chemistry, manufacturing and controls section of your application as a result of outstanding bioequivalence deficiencies must be submitted and could result in the response being considered a MAJOR Amendment.

Sincerely yours,

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

MB

August 12, 2002

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AB

BIOEQUIVALENCY AMENDMENT

RE: Butorphanol Tartrate Nasal Spray
10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, of Ontario, Canada, is hereby forwarding in duplicate a bioequivalency amendment in response to the FDA bioequivalency deficiency letter dated May 9, 2002.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

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AUG 16 2002
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NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

August 09, 2002

Mr. Steven Mazzella
Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Mazzella:

Re: BIOEQUIVALENCY AMENDMENT
Butorphanol Tartrate Nasal Spray 10 mg/mL, ANDA #75-499

Further to your Bioequivalency Amendment letter dated May 09, 2002, we are pleased to provide you with our responses in duplicate (Archival and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

You used two expired lots of the reference product (lot #M8K050B, EXP. December/2000 and lot #9F5910, EXP. June/2001) at the time of Droplet Size Distribution testing (3/2002). Therefore, the testing results for D50 and SPAN are invalid.

Response: In response to the above-noted deficiency, we have obtained three additional, unexpired lots of the reference listed drug (Stadol® NS) in order to repeat the required Droplet Size Distribution analysis. The Lot Nos. and expiry dates of the products tested are tabulated below:

Expiry Dates of Reference Products Used in Repeat Droplet Size Distribution Analysis		
Lot No.	**Expiry Date**	**Quantity Analyzed**
1F43643*	June 2003	10

.../cont'd

1F43639*	June 2003	10
1C52465*	March 2003	10

* New RLD lot

The individual droplet size distribution data for all pumps at various distances to the laser beam have been included in Attachment No. 3 of this amendment. A comparative summary table including the ratio of mean D values between the Novex Pharma and RLD has also been submitted as Attachment No. 3 to demonstrate that the droplet size distribution for the test product is within the range of 0.90-1.10.

The spray duration data corresponding to the droplet size distribution data acquisition has been included in Attachment No. 4. In addition, 20% of the obscuration/transmission vs. time plots are enclosed as Attachment No. 5. Lastly, a copy of the test method used for this analysis (GM-143) can be found in Attachment No. 6.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 884-2050, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:mt

Encl.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

August 13, 2002

ORIG AMENDMENT
N/AM

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

MINOR AMENDMENT

RE: Butorphanol Tartrate Nasal Spray 10 mg/mL
ANDA No. 75-499

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, of Ontario, Canada, is hereby forwarding in duplicate a minor amendment in response to FDA letter dated May 20, 2002.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
AUG 2 0 2002
OGD / CDER