CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-824

Generic Name: Butorphanol Tartrate Nasal Spray, 10 mg/ mL

Sponsor: Roxane Laboratories, Inc.

Approval Date: March 12, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-824

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CENTER FOR DRUG EVALUATION AND RESEARCH

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75-824

APPROVAL LETTER

ANDA 75-824

MAR 12 2002

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
1809 Wilson Road
Columbus, OH 43228

Dear Madam:

This is in reference to your abbreviated new drug application dated March 24, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Butorphanol Tartrate Nasal Spray, 10 mg/mL, (1 mg/spray), packaged in 2.5 mL metered-dose spray pumps.

Reference is also made to your amendments dated December 18, 2000; October 8, 2001; and January 17, February 1, and February 7, 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 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 FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 3/12/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-824

Final Printed Labeling

BUTORPHANOL TARTRATE Ⓒ
Nasal Spray

APPROVED
MAR 12 2002

4043300//03

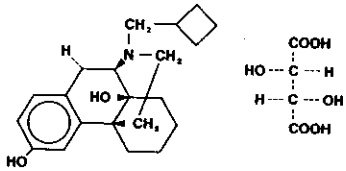
ROXANE LABORATORIES, INC.

BUTORPHANOL TARTRATE Ⓒ
Nasal Spray

R_x only

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-dihydroxybutanedioate (1:1) (salt). The molecular formula is $C_{21}H_{29}NO_2 \cdot C_4H_6O_6$, which corresponds to a molecular weight of 477.55 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 and/or hydrochloric acid added to adjust the pH to 5.0. The pump reservoir must be fully primed (see **PATIENT INSTRUCTIONS**) prior to initial use. After initial priming each metered spray delivers an average of 1.0 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 the κ-opioid receptors.

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

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

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

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

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

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

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

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

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

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 [illegible]

analgesia.

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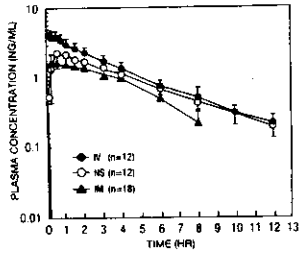
Pharmacokinetics

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

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



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 Bioavailability (%)			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 ^{3}H 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] as 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 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 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 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 [illegible] 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 1 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, patient 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.

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 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

In patients with hepatic or renal impairment, the initial dose sequence of butorphanol tartrate nasal spray 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 at intervals of no less than at 6 hours (see **CLINICAL PHARMACOLOGY: Pharmacokinetics and Individualization of Dosage** section) .

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 or 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 tartrate nasal spray (see Patient Instruction Leaflet and Medication Guide).

Drug Interactions

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

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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**).

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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 tartrate nasal spray (see Patient Instruction Leaflet and Medication Guide).

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 coadministration 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% decreases 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 coadministration with butorphanol tartrate nasal spray. These results suggest that the analgesic effect of butorphanol tartrate nasal

...mount of the salt is equivalent to 0.68 mg of the free base. The n-octanol/aqueous buffer partition coef-

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 coadministration of cimetidine (300 mg QID). Conversely, the administration of butorphanol tartrate nasal spray (1 mg butorphanol QID) did not alter the phamacokinetics of a 300 mg dose of cimetidine.

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

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 Use in Ambulatory Patients subsection above, and also see the Patient Instruction Leaflet and Medication Guide.

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. typhmurium* 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: Teratogenic Effects: 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 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 to 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
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 and butorphanol tartrate injection 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.

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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: Post Marketing 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, the use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, in patients with hepatic or renal disease, or in labor requires extra caution (see **PRECAUTIONS** section and **Individualization of Dosage** in **CLINICAL PHARMACOLOGY** section). 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.

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 vial containing a 2.5 mL bottle of nasal spray solution (10 mg/mL) and a metered-dose spray pump with protective clip and dust cover, a bottle of nasal spray solution, and a patient instruction leaflet and medication guide. On average, one bottle will deliver 14 to 15 doses if no repriming is necessary.

NDC 0054-3090-36 10 mg/mL, 2.5 mL bottle.

Storage Conditions

Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

[1]IMITREX® is a registered trademark of Glaxo-Wellcome, Inc.

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 with patient instruction leaflet and medication guide.

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3. Return the butorphanol tartrate nasal spray bottle to the child-resistant prescription vial for dispensing to the patient with patient instruction leaflet and medication guide.

MEDICATION GUIDE for BUTORPHANOL TARTRATE Nasal Spray

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 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 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 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 you 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 heartbeat 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.

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- Spray ***one*** **spray** in 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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- 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 you 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.
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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 you 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.

4043300//03

Revised January 2002

Roxane

MLB

NDC 0054-3090-36 2.5 mL

BUTORPHANOL TARTRATE

Nasal Spray

10 mg per mL

For Nasal Use Only

Rx only

APPROVED

MAR 12 2002

Roxane Laboratories, Inc. Columbus, Ohio 43216

Each mL contains 10 mg butorphanol tartrate and the following inactive ingredients: sodium chloride, citric acid, sodium hydroxide, hydrochloric acid for pH adjustment, benzethonium chloride and purified water.

Usual Dosage: Read enclosed circular for dosage information and patient instructions.

4077872/01 © RLI, 2001

EXP. LOT

MLB

NDC 0054-3090-36

2.5 mL Bottle and Spray Pump

LOT
EXP.

BUTORPHANOL TARTRATE

Nasal Spray

Rx Only

C IV

10 mg per mL

Spray ONCE into ONE nostril only.

DO NOT spray into both nostrils unless directed by your physician.

ATTENTION PHARMACIST:
PLEASE REMOVE THE TAMPER EVIDENT SEAL.
ASSEMBLE UNIT PRIOR TO DISPENSING.
REMOVE PACKAGE INSERT FROM CHILD-RESISTANT CONTAINER BEFORE DISPENSING. DO NOT REMOVE PATIENT INSTRUCTIONS AND MEDICATION GUIDE FROM CHILD-RESISTANT CONTAINER LABEL.

4077873//01

Roxane Laboratories, Inc.
Columbus, Ohio 43216

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-824

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1 2. ANDA # 75824

3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories, Inc.
Attention: Sean Alan F.X. Reads, M.A.
P.O. Box 16532
Columbus, Ohio 43216-6532

4. LEGAL BASIS FOR SUBMISSION
The RLD is Stadol®NS™ (Butorphanol Tartrate) Nasal Spray, 10 mg/mL, manufactured by Bristol Myers Squibb. There is no unexpired exclusivity for the listed drug. U.S. patent 4,464,378 for RLD will expire on 8/7/2001.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Butorphanol Tartrate Nasal Spray

8. SUPPLEMENT(s) PROVIDE(s) FOR:
None

9. AMENDMENTS AND OTHER DATES:
3/24/2000 - Original Submission
4/19/2000 - Acknowledgement Letter

10. PHARMACOLOGICAL CATEGORY
Narcotic
Mixed Agonist-Antagonist

11. Rx or OTC
Rx

APPEARS THIS WAY
ON ORIGINAL

12. RELATED IND/NDA/DMF(s)

DMF Number	DMF Type	DMF Holder#*
[redacted]		

*# attachment XX1b contains all DMF LOAs.
**VP3/106+144G1

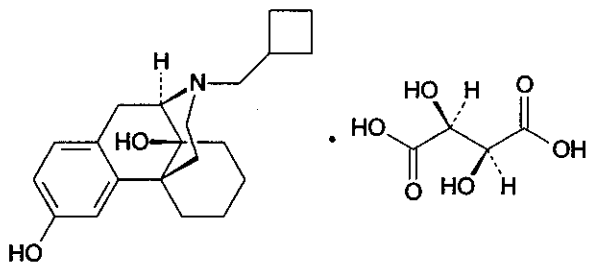
13. DOSAGE FORM
Nasal Spray

14. POTENCY
10 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Butorphanol Tartrate

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



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
None.

17. COMMENTS

The drug product has no compendial monograph, therefore, a MV will be requested. Labeling review reported as unacceptable dated 5/3/00.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend not approvable letter to issue (Major).

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
July 21, 2000

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1. CHEMISTRY REVIEW NO. 2 2. ANDA # 75824

3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories, Inc.
Attention: Shahid Ahmed
P.O. Box 16532
Columbus, Ohio 43216-6532

4. LEGAL BASIS FOR SUBMISSION
The RLD is Stadol®NS™ (Butorphanol Tartrate) Nasal Spray, 10 mg/mL, manufactured by Bristol Myers Squibb. There is no unexpired exclusivity for the listed drug. U.S. patent 4,464,378 for RLD will expire on 8/7/2001.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Butorphanol Tartrate Nasal Spray

8. SUPPLEMENT(s) PROVIDE(s) FOR:
None

9. AMENDMENTS AND OTHER DATES:
03/24/2000 - Original submission
04/19/2000 - Acknowledgement letter
04/20/2000 - New Correspondence
09/08/2000 - Chemistry deficiency letter
10/23/2000 - Amendment
11/16/2000 - Bio deficiency letter
11/13/2000 - Labeling review, inadequate
11/20/2000 - New Correspondence

10. PHARMACOLOGICAL CATEGORY
Narcotic
Mixed Agonist-Antagonist

11. Rx or OTC
Rx

12. RELATED DMF(s)

#	Type	Holder#*
[redacted]		

*# attachment XX1b contains all DMF LOAs.

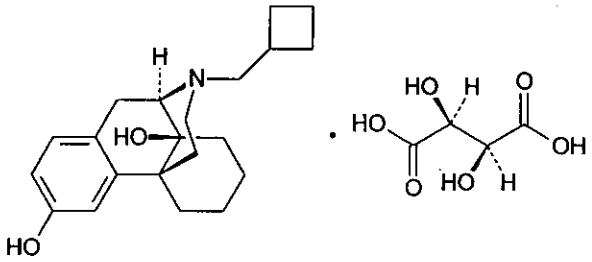
**VP3/106+144G1

13. DOSAGE FORM
Nasal Spray

14. POTENCY
10 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Butorphanol Tartrate
$C_{21}H_{29}NO_2 \cdot C_4H_6O_6$; M.W. 477.56



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b. (-)-17(cyclobutylmethyl)morphinan-3,14-diol [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt) CAS-58786-99-5

16. RECORDS AND REPORTS
None.

17. COMMENTS
The drug product has no compendial monograph, therefore, a MV was requested. Pending laboratory results (as of 4/6/01). Labeling review reported as unacceptable dated 11/13/00.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend not approvable letter to issue (facsimile).

19. REVIEWER: Edwin Ramos

DATE COMPLETED: April 7, 2001

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1. CHEMISTRY REVIEW NO. 4 2. ANDA # 75824

3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories
Attention: Elizabeth Ernst
P.O. Box 16532
Columbus, Ohio 43216-6532

4. LEGAL BASIS FOR SUBMISSION
The RLD is Stadol®NS™ (Butorphanol Tartrate) Nasal Spray, 10 mg/mL, manufactured by Bristol Myers Squibb. There is no unexpired exclusivity for the listed drug. U.S. patent 4,464,378 for the RLD expired on 8/7/2001.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Butorphanol Tartrate Nasal Spray

8. SUPPLEMENT(s) PROVIDE(s) FOR:
None

9. AMENDMENTS AND OTHER DATES:

3/24/2000 -	Original submission
4/19/2000 -	Acknowledgement letter
4/20/2000 -	New Correspondence
9/8/2000 -	Chemistry deficiency letter
9/23/2000 -	Amendment
11/16/2000 -	Bio deficiency letter
11/13/2000 -	Labeling review, inadequate
11/20/2000 -	New Correspondence
12/4/00-	Bio deficiency letter
12/18/00-	Bio Amendment
4/19/2001-	Facsimile
5/3/2001-	Amendment
9/19/01-	Amendment
10/23/01-	Amendment

10. PHARMACOLOGICAL CATEGORY
Narcotic
Mixed Agonist-Antagonist

11. Rx or OTC
Rx

12. RELATED DMF(s)

#	Type	Holder#*
[redacted]		

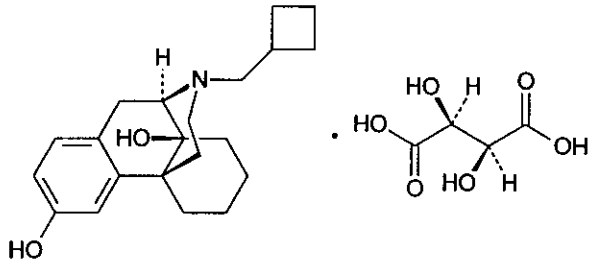
*# attachment XX1b contains all DMF LOAs.
**VP3/106+144G1

13. DOSAGE FORM
Nasal Spray

14. POTENCY
10 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Butorphanol Tartrate
$C_{21}H_{29}NO_2 \cdot C_4H_6O_6$; M.W. 477.56



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
None.

17. COMMENTS
The drug product has no compendial monograph. MV reported as suitable for regulatory purposes dated 3/15/01. Labeling review reported as acceptable dated 5/16/01.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approvable - pending on EER.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
October 15, 2001
October 23, 2001(revised)

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1. CHEMISTRY REVIEW NO. 5 2. ANDA # 75824

3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories
Attention: Shahid Ahmed
P.O. Box 16532
Columbus, Ohio 43216-6532

4. LEGAL BASIS FOR SUBMISSION
The RLD is Stadol®NS™ (Butorphanol Tartrate) Nasal Spray, 10 mg/mL, manufactured by Bristol Myers Squibb. There is no unexpired exclusivity for the listed drug. U.S. patent 4,464,378 for the RLD expired on 8/7/2001.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Butorphanol Tartrate Nasal Spray

8. SUPPLEMENT(s) PROVIDE(s) FOR:
None

9. AMENDMENTS AND OTHER DATES:

3/24/2000 -	Original submission
4/19/2000 -	Acknowledgement letter
4/20/2000 -	New Correspondence
9/8/2000 -	Chemistry deficiency letter
9/23/2000 -	Amendment
11/16/2000 -	Bio deficiency letter
11/13/2000 -	Labeling review, inadequate
11/20/2000 -	New Correspondence
12/4/00-	Bio deficiency letter
12/18/00-	Bio Amendment
4/19/2001-	Facsimile
5/3/2001-	Amendment
9/19/01-	Amendment
10/8/01	Amendment
10/23/01	Chemistry Review
10/23/01	Gratuitous Amendment
11/13/01	Bio Review adequate
12/18/01-	Deficiency letter
1/17/02-	Gratuitous Amendment
2/1/02-	Minor Amendment
2/7/02-	Amendment

10. PHARMACOLOGICAL CATEGORY
Narcotic
Mixed Agonist-Antagonist

11. Rx or OTC
Rx

12. RELATED DMF(s)

#	Type	Holder#*
[redacted]		

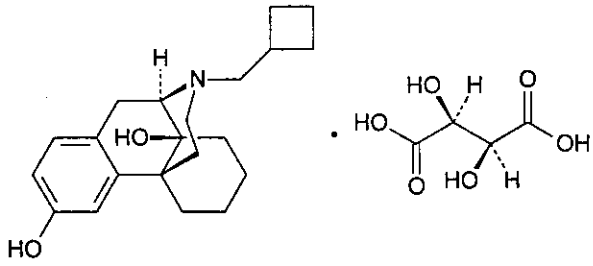
*# attachment XX1b contains all DMF LOAs.
**VP3/106+144G1

13. DOSAGE FORM
Nasal Spray

14. POTENCY
10 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Butorphanol Tartrate
$C_{21}H_{29}NO_2 \cdot C_4H_6O_6$; M.W. 477.56



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
None.

17. COMMENTS
The drug product has no compendial monograph. MV reported as suitable for regulatory purposes dated 3/15/01. EER reported as adequate dated 2/15/02.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approvable letter to issue.

19. REVIEWER:
Edwin Ramos

/S/

DATE COMPLETED:
February 28, 2002

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DIVISION REVIEW SUMMARY

ANDA: 75-824

DRUG PRODUCT: Butorphanol Tartrate

FIRM: Roxane Labs
DOSAGE FORM: Nasal Spray
STRENGTH: 10 mg/mL
CONTAINER: 2.5 mL fill in a 5 mL amber, round, v-shaped bottom, vial

CGMP STATEMENT/EIR UPDATE STATUS:
Acceptable dated 02/15/02.

BIO INFORMATION:
Bio review acceptable dated 11/13/01.

VALIDATION
Method validation for the finished drug product reported as adequate for regulatory purposes dated 3/15/01.

STABILITY
Lot number 9990001 was placed in accelerated (40°C/75% RH) and room temperature stability studies in the proposed marketing container configuration (with the cap and the pump in-place, stored inverted and on its side). 24 months of updated room temperature stability data is included. The stability data appended are found to conform to the proposed stability specifications. Based upon the stability data submitted, the proposed 24 months expiration period for the finished product is granted.

The proposed marketing container configuration is fully described in the container section of the application.

LABELING
Acceptable dated 5/16/01.

STERILIZATION VALIDATION
Not applicable.

SIZE OF BIO/STABILITY BATCHES
Butorphanol Tartrate is manufactured by [redacted]

DMF [redacted] was reviewed and found to be adequate on 4/30/01.

A [redacted] demonstration batch was manufactured. A total of [redacted] were packaged. A total of [redacted] were filled.

PROPOSED PRODUCTION BATCH
BBR for the intended production batch size of [redacted] is included.

Butorphanol Tartrate Tests and Specification (p 10, 5/3/01)

Description	White powder
Identification	. The [redacted] of the sample corresponds to that of the std
Assay	[redacted]
Specific Rotation	
[redacted]	NMT [redacted]
Residue on Ignition	NMT [redacted]
[redacted]	NMT [redacted]
Total Impurities [redacted]	NMT [redacted]
Total Impurities [redacted]	NMT [redacted]
Related Compounds	
[redacted]	NMT [redacted]
[redacted]	NMT
Single largest unknown	NMT [redacted]
Residual Solvents	[redacted] NMT [redacted]
	[redacted] NMT [redacted]
	[redacted] NMT [redacted]
Microbial Limit Test	
Total [redacted] plate count	[redacted]

(p 49, 5/3/01)

Test	Specification
Physical Appearance	Clear colorless solution
PH	[redacted]
Osmolality	[redacted]
Density	[redacted]

APPEARS THIS WAY
ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-824

BIOEQUIVALENCE REVIEW

Butorphanol Tartrate
Nasal Spray, 10 mg/mL
ANDA #75-824
Reviewer: James E. Chaney
V:\FIRMSNZ\ROXANE\LTRS&REV\75824w.300

Roxane Laboratories
Columbus, Ohio
Submission Date:
March 24, 2000

Review of In Vitro Data and Waiver Request

1. Introduction:

The demonstration of bioequivalence of aqueous solution nasal sprays may be accomplished based on: a) Q1 and Q2 sameness of the generic and innovator formulations, and b) equivalent *in vitro* performance of the test product to the reference product.

The comparative performance of the drug delivery devices of the test and reference products may be based on the following tests:

Unit Dose/Content Uniformity
Spray Pattern
Plume Geometry
Droplet Size Distribution by at least two methods
Priming, Loss of Prime, and Tail-Off

The firm has submitted comparative formulation data of its proposed test product and the reference listed drug Stadol® Nasal Spray, 10 mg/mL. The firm conducted comparative *in vitro* testing on the following parameters: unit dose/ content uniformity, spray pattern, plume geometry, droplet size distribution (laser diffraction and cascade impactor), priming, re-priming and tailing-off.

2. 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 administered using a manual metering device. The product is marketed as a solution provided in 2.5 mL fill bottles. Following priming a 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.

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

Comparative formulations of the reference and the proposed test product are given in Table 1. 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.

4. Drug Products:

Test: Roxane's Butorphanol Nasal Spray, 10 mg/mL. Batch # 999001A of the solution formulation was used for all three sub-lots. Batch size was [redacted], commercial scale, [redacted] which yielded [redacted] Solution manufactured March 1, 1999; proposed expiration dating is 24 months. The sub-lot numbers were V203079500, V203830900 and V204011600 corresponding to different pumps.

Reference: Bristol-Meyers Squibb's Stadol NS®, 10 mg/mL; Lots 9F10028, 9F13540 and 9F15910. For the reference product, it is not known if the drug product and/or valves are from the same or different lots.

Comparability of Spray Devices

. developed and provided a nasal spray pump to Roxane Laboratories which was identical to that of the innovator product with the exception of a different was used in the test product instead of the , the exact details of which have not been disclosed to Roxane due to confidentiality reasons. , no longer offers the innovator's formulation as a standard pharmaceutical

Drawings of the nasal pump were included in the submission (Section XIII, Attachment XIIIe, pp 1095-1119 of Vol. 5).

5. Procedures and Information Applicable to All Tests

All actuations of the nasal spray products were done using an automatic actuator to actuate the nasal sprays in a reproducible manner. The actuator was a proprietary unit designed by , for nasal spray actuation. The force used for actuation of the nasal sprays was specified at . by the sponsor. The Roxane samples consisted of one lot of the drug solution formulation and three lots of pumps. The pumps were assembled onto the bottles at time of testing for both the Roxane product and the Reference product.

For each *in-vitro* 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.

6. Unit Dose and Uniformity Of Unit Dose

6.1 Sampling Procedure

For the content uniformity portion of the bioequivalency study, 10 units from each lot of product were tested. The data sequence for the content uniformity testing was to record individual actuation weights for actuations 1 through 10 and 21 through 23. Actuations 7 through 10 and 21 through 23 were collected for assay. The assay values for actuations 8 and 21 were the data sources used to evaluate content uniformity of the product. Analytical method validation data shows that the nethod is linear, selective, accurate, precise (%CV=0.1%) and rugged. The assay is free from interference due to excipients, degradation products and related compounds of the proposed formulation. The assay of butorphanol tartrate has a range of the normal assay concentration of 1.0 mg/mL butorphanol (LOQ =

6.2 Results

The firm reported content uniformity summary results only for actuations 8 and 21. See Table 2 for the summary data for actuations 8, 9 and 23 as calculated by the reviewer . Overall variability (%CV) and range of within lot %CV's are presented in Table 3.

Comments:

- The firm reported "Beginning" as Actuation # 8 in its summary data. The reviewer calculated summary data for actuation # 9 in addition to # 8 because the patient instructions recommend priming until a fine spray appears (up to 7 to 8 strokes). The reviewer's calculations provided grand mean (N=30) values in addition to mean values for lots. The firm had reported only mean values for lots in its summary data (N=10). The reviewer's means agree with firm's means (N=10).

- Also, the reviewer did the calculations for actuation # 23 that would correspond to the 15th actuation from actuation # 9 in that a bottle delivers 14-15 sprays per the labeling.
- The minimum and maximum values for the test and reference products show that the delivered doses fall within 88-113% 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 of the label claim, and none should be outside the
- The differences in the test and reference products at actuation #9 (beginning of unit life) and actuation #23 (end of unit life) are not statistically significant, and the differences in mean (N=30) values are less than or equal to 2.1%. The difference between the test and reference products at actuation #8 (beginning of unit life) is statistically significant. However, the difference in the mean (N=30) values between test and reference is only 1.7%.
- The overall variability and within lot variability are very low and similar for the test and reference products (5.9 %CV or less, Table 3).

7. Spray Pattern

7.1 Method

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6. [redacted]

15. Recommendation:

The waiver request of *in vivo* bioequivalence requirements for the test product, Roxane Laboratories on its Butorphanol Tartrate Nasal Spray Pump, 10 mg/mL, is denied due to the reasons cited in the above deficiencies.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 11/16/2000

Concur: /S/ Date 11/29/00
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/111600
V:\FIRMSNZ\ROXANE\LTRS&REV\75824w.300

Table 1. Formulation (mg/mL), [NOT TO BE RELEASED UNDER FOI]		
Ingredient	**Test**	**Reference**
Butorphanol Tartrate	10	10
Sodium Chloride	[redacted]	[redacted]
Citric Acid	[redacted]	[redacted]
Benzethonium Chloride	[redacted]	[redacted]
Sodium Hydroxide	Adjust pH	Adjust pH
Hydrochloric Acid	Adjust pH	Adjust pH
Water, Purified	Q.S.	Q.S.
PH	5	5

Table 2. Content Uniformity (mg Delivered/Actuation)								
	Statistic	**N**	**Test (mg/Spray)**		**Reference (mg/Spray)**		**T/R**	***P***
			Sub-Lot #	Mean	Lot #	Mean		
Beginning (Spray #8)		10	V203079500	1.039	9F10028	1.053	0.986	
		10	V203830900	1.034	9F13540	1.074	0.963	
		10	204011600	1.078	9F15910	1.078	1.000	
	Grand Mean	30		1.050		1.068	0.983	*0.040*
	%CV	30		4.8		2.8		
	Min	30	[redacted]					
	Max	30						
Beginning (Spray #9)		10	V203079500	1.026	9F10028	1.068	0.961	
		10	V203830900	1.032	9F13540	1.046	0.987	
		10	204011600	1.088	9F15910	1.085	1.002	
	Grand Mean	30		1.049		1.066	0.983	*0.068*
	%CV	30		4.7		4.5		
	Min	30	[redacted]					
	Max	30						
End (Spray #23)		10	V203079500	1.061	9F10028	1.069	0.992	
		10	V203830900	1.039	9F13540	1.077	0.964	
		10	204011600	1.050	9F15910	1.072	0.980	
	Grand Mean	30		1.050		1.073	0.979	*0.434*
	%CV	30		4.0		3.8		
	Min	30	[redacted]					
	Max	30						

Table 3. Overall Variability (%CV) and Range of Within Lot Variability (%CV) from Content Uniformity Data.		
	Overall Variability	**Range of Within Lot %CV's**
Test	4.0-4.8	1.2-6.3
Reference	2.8-4.5	1.4-5.9

Table 4. Spray Pattern Testing Data: Calculated from the Pattern Center (N=30)						
Distance (cm)	**Stage**	**Product**	**Statistic**	**Dmax (mm)**	**Dmin (mm)**	**Ovality Ratio**
3	Begin	Test	Mean	37.510	32.859	1.147
			%CV	7.8	9.1	8.4
		Reference	Mean	35.904	31.278	1.159
			%CV	10.0	8.6	16.6
			T/R	1.045	1.051	0.990
			P	*0.02393*	*0.00575*	*0.38019*
	End	Test	Mean	38.414	34.386	1.121
			%CV	8.3	10.2	5.8
		Reference	Mean	36.345	32.200	1.136
			%CV	9.8	8.6	13.6
			T/R	1.057	1.068	0.987
			P	*0.00452*	*0.00241*	*0.29922*
4	Begin	Test	Mean	45.660	37.728	1.214
			%CV	9.3	8.9	8.8
		Reference	Mean	41.304	34.162	1.223
			%CV	12.9	10.2	19.5
			T/R	1.105	1.104	0.993
			P	*0.00055*	*0.00011*	*0.42132*
	End	Test	Mean	46.282	38.705	1.199
			%CV	8.9	8.5	8.1
		Reference	Mean	42.336	35.455	1.212
			%CV	12.1	11.3	20.2
			T/R	1.093	1.092	0.990
			P	*0.00066*	*0.00121*	*0.39316*
5	Begin	Test	Mean	54.670	43.265	1.266
			%CV	11.2	7.3	10.6
		Reference	Mean	48.037	37.455	1.305
			%CV	15.3	14.6	21.9
			T/R	1.138	1.155	0.970
			P	*0.00008*	*0.00000*	*0.22806*
	End	Test	Mean	55.927	44.913	1.249
			%CV	11.1	10.1	9.1
		Reference	Mean	49.141	39.039	1.284
			%CV	13.8	11.9	23.6
			T/R	1.138	1.150	0.973
			P	*0.00011*	*0.00003*	*0.27083*

Table 5. Overall Variability (%CV) and Range of Within Lot Variability (%CV) From Spray Pattern Data.						
	Overall Variability			Range of Within Lot %CV's		
	Dmax	Dmin	Ovality	Dmax	Dmin	Ovality
Test	7.8-11.2	7.3-10.2	5.8-10.6	3.0-14.6	4.0-12.6	2.9-12.3
Reference	7.8-15.3	8.6-14.6	13.6-23.6	6.6-21.0	5.0-16.2	5.4-28.0

Table 6. Plume Geometry Data (N=30)						
Time (ms)	**View**	**Product**	**Statistic**	**Length (cm)**	**Width (cm)**	**Angle (°)**
20	Front	Test	Mean	15.59	11.26	60.9
			%CV	9.9	13.9	10.9
		Reference	Mean	15.55	10.49	58.5
			%CV	14.3	13.5	10.3
			T/R	1.003	1.074	1.041
			p	*0.470*	*0.024*	*0.072*
	Side	Test	Mean	15.33	11.55	61.5
			%CV	10.4	12.9	10.0
		Reference	Mean	15.557	10.21	58.5
			%CV	13.7	13.4	7.2
			T/R	0.985	1.131	1.051
			p	*0.332*	*0.002*	*0.020*
75	Front	Test	Mean	28.18	16.49	54.6
			%CV	7.2	14.4	13.4
		Reference	Mean	28.63	15.66	50.7
			%CV	7.1	14.0	14.6
			T/R	0.984	1.053	1.076
			p	*0.208*	*0.095*	*0.026*
	Side	Test	Mean	28.19	16.75	54.0
			%CV	7.1	12.6	13.4
		Reference	Mean	28.86	15.32	51.2
			%CV	8.6	12.3	15.5
			T/R	0.977	1.094	1.056
			P	*0.146*	*0.009*	*0.078*
150	Front	Test	Mean	37.33	18.56	54.3
			%CV	8.0	12.9	13.8
		Reference	Mean	38.58	17.24	49.8
			%CV	4.5	13.3	11.7
			T/R	0.967	1.077	1.090
			P	*0.027*	*0.026*	*0.013*
	Side	Test	Mean	36.97	18.88	54.6
			%CV	7.1	11.7	13.0
		Reference	Mean	38.56	17.10	50.3
			%CV	5.0	10.0	9.3
			T/R	0.959	1.105	1.085
			P	*0.006*	*0.004*	*0.009*

Table 7. Overall Variability (%CV) and Range of Within Lot Variability (%CV) From Plume Geometry Data.						
	Overall Variability			Range of Within Lot %CV's		
	Length	Width	Angle	Length	Width	Angle
Test	7.1-10.4	11.7-14.4	10.0-13.8	5.8-11.7	5.4-16.9	7.0-17.1
Reference	4.5-14.3	10.0-14.0	7.2-15.5	3.4-19.6	5.3-17.5	4.9-19.3

Table 8. Firm's Reported Plume Geometry Data for Test Product

Butorphanol Tartrate Summary						
	Plume angle, 20 ms		Plume length, 75 ms		Plume Width, 75 ms	
Pump Number	Front	Side	Front	Side	Front	Side
V204011600 Average	63.5	63.8	28.5	28.3	17.4	18.4
%RSD	8.7	9.5	8.7	7.4	9.0	10.0
V203079500 Average	59.6	61.4	28.6	28.8	15.0	15.4
%RSD	9.7	7.0	6.8	7.6	12.7	5.4
V203830900 Average	59.7	59.3	27.4	27.5	17.1	16.4
%RSD	13.9	12.7	5.8	5.8	16.9	13.6

Table 9. Firm's Reported Plume Geometry Data for Reference Product

Stadol NS Summary						
	Plume angle, 20 ms		Plume length, 75 ms		Plume width, 75 ms	
Lot Number	Front	Side	Front	Side	Front	Side
9F13540 Average	56.3	58.1	29.7	29.4	14.9	15.5
%RSD	7.9	4.9	5.6	4.0	12.1	9.7
9F15910 Average	58.7	57.9	27.8	27.9	15.1	14.3
%RSD	14.4	10.5	8.3	13.1	17.5	11.9
9F10028 Average	60.6	59.6	28.5	29.4	17.0	16.1
%RSD	6.7	5.6	6.1	6.2	9.0	13.1

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Table 10. Droplet Size Distribution Determined By [redacted] Diffraction At Beginning, Middle And End Stages (N=30).

Stage of Unit Life	Distance (cm)	Delay Time (ms)	D_{50}						SPAN					
			Test		Reference				Test		Reference			
			Mean	%CV	Mean	%CV	T/R	*p*	Mean	%CV	Mean	%CV	T/R	*p*
Begin	1	15	53.08	15.2	57.28	12.9	0.93	0.026	1.64	6.0	1.72	9.9	0.95	0.012
Begin	1	45	59.81	12.0	64.91	18.6	0.92	0.025	1.53	5.8	1.63	9.2	0.94	0.004
Begin	1	75	72.95	39.3	70.61	27.3	1.03	0.364	1.54	9.7	1.67	18.2	0.92	0.021
Begin	3	15	45.24	15.3	46.71	14.5	0.97	0.209	1.65	6.3	1.71	25.1	0.96	0.232
Begin	3	45	50.33	13.2	54.42	13.4	0.92	0.016	1.60	4.4	1.62	24.1	0.98	0.348
Begin	3	75	66.02	45.4	63.92	28.4	1.03	0.385	1.57	6.8	1.58	9.1	0.99	0.325
Begin	5	15	40.76	12.6	43.92	9.9	0.93	0.003	1.45	11.1	1.44	14.4	1.00	0.469
Begin	5	45	46.35	12.9	51.95	11.2	0.89	0.000	1.37	10.3	1.36	11.8	1.01	0.368
Begin	5	75	58.20	43.8	64.40	42.4	0.90	0.207	1.46	12.4	1.45	22.2	1.01	0.447
Mean Begin Stage			**54.75**	**19.1**	**57.57**	**15.7**	**0.95**	--	**1.53**	**6.1**	**1.58**	**8.3**	**0.97**	--
Middle	1	15	51.57	13.5	57.04	15.5	0.90	0.009	1.62	4.8	1.94	47.8	0.83	0.033
Middle	1	45	57.93	13.2	61.94	12.3	0.94	0.032	1.53	4.4	1.71	19.2	0.90	0.004
Middle	1	75	62.08	11.7	65.14	12.9	0.95	0.073	1.53	3.6	1.86	45.7	0.82	0.023
Middle	3	15	42.14	14.6	45.83	14.4	0.92	0.004	1.66	6.1	1.64	14.8	1.01	0.408
Middle	3	45	49.62	17.0	52.47	13.6	0.95	0.049	1.56	6.3	1.55	7.2	1.01	0.231
Middle	3	75	56.47	19.5	57.22	13.2	0.99	0.370	1.56	6.4	1.50	7.5	1.04	0.011
Middle	5	15	41.76	11.2	44.51	14.3	0.94	0.033	1.49	10.3	1.49	23.0	1.01	0.453
Middle	5	45	48.27	11.2	51.80	11.9	0.93	0.007	1.40	11.1	1.38	24.3	1.01	0.408
Middle	5	75	53.10	27.8	55.81	11.8	0.95	0.163	1.43	15.0	1.42	21.2	1.01	0.419
Mean Middle Stage			**51.44**	**13.3**	**54.64**	**12.5**	**0.94**	--	**1.53**	**5.4**	**1.61**	**12.1**	**0.95**	--
End	1	15	52.49	10.9	58.10	16.1	0.90	0.002	1.63	5.5	2.10	52.4	0.78	0.013
End	1	45	58.44	11.1	63.75	15.9	0.92	0.009	1.56	5.6	1.76	29.9	0.89	0.022
End	1	75	68.01	57.5	67.22	17.1	1.01	0.457	1.55	7.4	1.72	27.7	0.90	0.029
End	3	15	44.63	15.0	47.32	18.4	0.94	0.096	1.64	7.1	1.75	17.1	0.94	0.025
End	3	45	50.79	14.8	54.01	16.7	0.94	0.076	1.56	7.1	1.62	12.4	0.97	0.094
End	3	75	58.35	25.3	58.98	16.6	0.99	0.428	1.59	9.4	1.58	10.6	1.01	0.360
End	5	15	41.41	11.5	42.14	11.5	0.98	0.291	1.53	7.1	1.56	17.0	0.98	0.271
End	5	45	48.19	13.6	50.05	12.5	0.96	0.155	1.42	6.2	1.48	23.4	0.96	0.221
End	5	75	57.77	51.2	53.84	11.4	1.07	0.239	1.45	11.5	1.50	25.7	0.97	0.291
Mean End Stage			**53.34**	**15.4**	**55.05**	**14.4**	**0.97**	--	**1.55**	**4.7**	**1.67**	**11.4**	**0.93**	--

Table 11. Overall Variability (%CV) and Range of Within Lot Variability (%CV) From Droplet Size Distribution Determined by [redacted] at Beginning, Middle and End Stages.				
	Overall Variability		Range of Within Lot %CV's	
	D_{50}	SPAN	D_{50}	SPAN
Test	10.9-57.5	3.6-15	5.5-89.0	2.3-18.9
Reference	9.9-42.4	7.2-52.4	7.2-59.5	2.7-58.0

Table 12. Mean Recovery Data From Five Actuations In Cascade Impaction Study (N=30).									
		Test			Reference				
Sector	Group	Mean	%CV	%/Group	Mean	%CV	%/Group	T/R	*P*
BEGIN	1	5188.83	4.6	0.993	5141.90	10.8	0.992	1.01	*0.34085*
	2	5.21	29.6	0.001	6.84	103.6	0.001	0.76	*0.10733*
	3	33.57	33.7	0.006	34.56	38.4	0.007	0.97	*0.37782*
END	1	4952.02	6.2	0.993	4979.39	4.7	0.992	0.99	*0.34337*
	2	4.01	34.1	0.001	4.59	42.4	0.001	0.87	*0.11064*
	3	30.43	40.0	0.006	33.64	39.2	0.007	0.90	*0.14931*

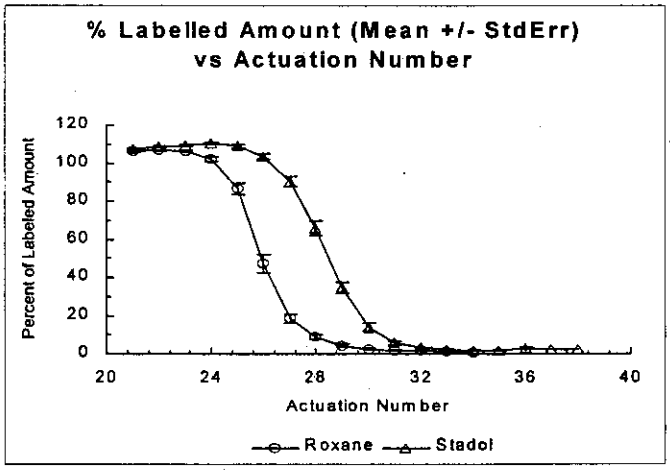
Table 13. Overall Variability (%CV) and Range of Within Lot Variability (%CV) from Recovery Data Following Five Actuations in Cascade Impaction Study.		
	Overall Variability	Range of Within Lot %CV's
Test	4.6-40	1.3-37.5
Reference	4.7-103.6	2.5-136.0

Table 14. Summary of μG Butorphanol Tartrate Per Actuation As Reported By The Firm				
	Beginning of Life		End of Life	
	Roxane	Stadol NS®	Roxane	Stadol NS®
Globe	[redacted]			
Adaptor				
Preseparator				
Sum (Group 1)				
Stage 0 (Group 2)				
Stages 1-7 (Group 3)				

Table 15. Priming/ Repriming Data (mg/Spray)								
	Test			Reference				
Spray #	Mean	%CV	N	Mean	%CV	N	T/R	*p*
7	1.045	6.37	30	1.082	3.81	30	0.966	0.00631
8	1.068	2.84	30	1.076	4.35	30	0.993	0.205262
9	1.049	4.76	30	1.066	4.47	30	0.983	0.068211
12	1.061	3.44	30	1.082	2.43	30	0.980	0.004452
13	1.073	3.15	30	1.098	1.75	30	0.977	0.000533

Table 16. Tail Off Data (mg/spray)							
	Test			Reference			
Spray #	Mean	%CV	N	Mean	%CV	N	T/R
21	1.061	2.98	30	1.073	4.81	30	0.989
22	1.066	2.49	30	1.088	3.56	30	0.980
23	1.062	2.29	30	1.094	2.81	30	0.971
24	1.023	6.26	30	1.107	2.58	30	0.924
25	0.865	19.20	30	1.090	3.89	30	0.794
26	0.470	53.71	30	1.035	8.33	30	0.454
27	0.185	69.12	30	0.903	15.93	30	0.205
28	0.090	62.31	29	0.659	30.84	30	0.137
29	0.045	87.35	29	0.347	47.82	30	0.128
30	0.026	90.67	24	0.139	85.57	30	0.189
31	0.021	72.91	19	0.058	77.75	30	0.359
32	0.019	50.70	7	0.033	52.31	28	0.584
33	0.010	88.88	3	0.026	72.09	24	0.384
34	0.005	-	1	0.020	78.52	17	0.249
35	0.000	-	0	0.020	46.16	8	0.000
36	0.000	-	0	0.028	26.95	2	0.000
37	0.000	-	0	0.026	-	1	0.000
38	0.000	-	0	0.025	-	1	0.000

Figure 1. Plot of Tail Off Data



DEC 4 2000

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-824 APPLICANT: Roxane Laboratories

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. Please report expiration dates for the three lots of reference product.
2. Please submit representative (at least 20%) computer printout sheets for the [redacted]
3. [redacted] raw data to the Agency for evaluation.
4. Regarding the actuators you did not supply the following information on the test and reference products [redacted]. Please supply this information.
5. Please provide evidence of rationale for selecting [redacted] as delay times for characterizing [redacted] respectively. The evidence may include plots of percent obscuration or percent transmission as a function of time (ms).
6. You submitted only a hard copy of the raw plume data. In future applications on this dosage form you should submit diskettes of the raw plume data in Microsoft Excel.

Sincerely yours,

/S/

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

CC: ANDA 75-824
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney /S/ 11/16/2000
HFD-652/ Y. Huang /S/ 11/16/2000
HFD-655/ GJP Singh /S/ 11/20/00
HFD-617/ K. Scardi
for HFD-650/ D. Conne /S/ 11/29/00

V:\FIRMSNZ\ROXANE\LTRS&REV\75824w.300

BIOEQUIVALENCY - DEFICIENCY Submission Date: March 24, 2000

~~**WAIVER (WAI)**~~
Testing Laboratory:
OTHER (OTH)
- in vitro testing

Strengths 10 mg/mL
Outcome: **IC**

NOTE:
AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: **Incomplete**

WINBIO COMMENTS:

The *in vitro* performance testing conducted on Roxane Laboratories' Butorphanol Tartrate Nasal Spray Pump, 10 mg/mL comparing it with the reference product, Stadol®, nasal solution (Bristol-Myers) has been found incomplete.

BIOEQUIVALENCY AMENDMENT

ANDA 75-824

DEC 4 2000

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: Roxane Laboratories, Inc. TEL: 614-241-4131

ATTN: Sean Alan F.X. Reade, M.A. FAX: 614-276-0321

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 24, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 10mg/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:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-824 SPONSOR : Roxane Laboratories
DRUG AND DOSAGE FORM: Butorphanol Tartrate Nasal Spray,
STRENGTH(S): 10 mg/mL
TYPES OF STUDIES: *In vitro*

TESTING LABORATORY: ———

STUDY SUMMARY: Acceptable

DISSOLUTION: NA

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status:	Inspection results: Acceptable
First Generic YES New facility NO For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date) Aug 01, 2001	

PRIMARY REVIEWER: James Chaney BRANCH: I

INITIAL: /S/ DATE: 5/21/2001

TEAM LEADER: Yih-Chain Huang BRANCH: I

INITIAL: /S/ DATE: 5/21/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

for INITIAL : /S/ DATE : 11/15/2001

Main - Jeca 3.1

Butorphanol Tartrate
Nasal Spray, 10 mg/mL
ANDA #75-824
Reviewer: James E. Chaney
V:\FIRMSNZ\ROXANE\LTRS&REV\75824a.D00

Roxane Laboratories
Columbus, Ohio
Submission Date:
December 18, 2000

REVIEW OF ADDENDUM TO ORIGINAL REVIEW OF MARCH 24, 2000 SUBMISSION AND AN AMENDMENT TO THE ORIGINAL DECEMBER 18, 2000 SUBMISSION

1. Addendum To Original Review Of The March 24, 2000 Submission

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 completely implemented at this time. The evaluation of the *in vitro* equivalence of the test- and reference product is based on ratios of geometric means and consideration of relative variability (%CV) of test and reference products. In the original review arithmetic means were presented. In this addendum the evaluation of the *in vitro* equivalence of test and reference products is based on ratios of geometric means.

1.1 Unit Spray Content (Unit Dose)

The test/reference geometric mean ratios for the unit spray content (unit dose) were within the limit of 90-111%, stipulated in the draft Nasal BA/BE guidance (Table 1). The variability of the test and reference products was comparable. The unit spray content data are acceptable.

[redacted]

1.3 Spray Pattern

With regard to the spray pattern data, the overall variability of the test product was lower than that of the reference product for the parameters Dmax, Dmin and ovality-ratios. The test/reference ratios of the geometric means were within the 90-111% range except ratios for the Dmax and Dmin data at the 5-cm distance (Table 3).

The spray pattern data were also analyzed by the population bioequivalence (PBE) approach outlined in the draft guidance. The statistical methodology based on that approach takes into consideration the relative variability of the test and reference products in determining product equivalence. The PBE analyses were performed by [redacted] (Attachment I).

Because values of two parameters (i.e., $sigma_{T0}$ - the variance terms offset, and epsilon – the scaling variance) to be used for the methodology outlined in the draft guidance are still under consideration [redacted] analysis of the spray pattern data utilized combinations (i.e., $sigma_{T0}$ values of 0.1 and 0.2, and epsilon values of 0.0, 0.01, 0.03, and 0.05, where 0.0 represents the most stringent criterion). In addition the average bioequivalence (ABE) limits of 1.11 and 1.25 were used. With the exception of the 5-cm Dmin data, the test product meets equivalence criterion based on all combinations of ABE, $sigma_{T0}$ and epsilon. However, based on an epsilon value of 0.01, the test product meets equivalence criteria for all three parameters at all three distances. Therefore, the spray pattern data are acceptable.

1.4 Droplet Size Distribution

In its December 18, 2000 amendment in response to deficiency 5 of the bioequivalence review of the original March 24, 2000 submission (See Response to Deficiency 5 in the Amendment section of this review) the sponsor submitted representative plots of %

[redacted]

nasal BA/BE guidance.

- The SPAN data were also analyzed in the manner outlined for the D50 data. Based on the analyses, T/R ratios were found to be within the acceptable range of 0.90-1.11.
- The total variability of the D50 data from the test product was comparable to that of the reference product. For the SPAN data, the test product was less variable than the reference product.
- As was done for the spray pattern data, the droplet size distribution data were also analyzed by [redacted] (Attachment II). The droplet size distribution data were determined to be acceptable.

1.5 Plume Geometry

Plume geometry was characterized by plume angle, plume height, and plume width for the front and side views of the plume (Table 5). Based on the test/reference geometric mean ratios of the front view data, plume geometric characteristics of the test and reference products are similar (i.e., with the limits of 90-111% stipulated in the draft Nasal BA/BE guidance).

1.6 AddendumTables

Table 1. Content Uniformity (mg Delivered/Actuation)								
	Statistic	N	Test (mg/Spray)		Reference (mg/Spray)		T/R	*P*
			Sub-Lot #	Mean	Lot #	Mean		
Beginning (Spray #8)		10	V203079500	1.039	9F10028	1.053	0.986	
		10	V203830900	1.034	9F13540	1.074	0.963	
		10	204011600	1.078	9F15910	1.078	1.000	
	Grand Mean	30		1.050 (1.049)		1.068 (1.068)	0.983 (0.983)	*0.040*
	%CV	30		4.8		2.8		
	Min	30						
	Max	30						
Beginning (Spray #9)		10	V203079500	1.026	9F10028	1.068	0.961	
		10	V203830900	1.032	9F13540	1.046	0.987	
		10	204011600	1.088	9F15910	1.085	1.002	
	Grand Mean	30		1.049 (1.048)		1.066 (1.066)	0.983 (0.983)	*0.068*
	%CV	30		4.7		4.5		
	Min	30						
	Max	30						
End (Spray #23)		10	V203079500	1.061	9F10028	1.069	0.992	
		10	V203830900	1.039	9F13540	1.077	0.964	
		10	204011600	1.050	9F15910	1.072	0.980	
	Grand Mean	30		1.050 (1.049)		1.073 (1.072)	0.979 (0.979)	*0.434*
	%CV	30		4.0		3.8		
	Min	30						
	Max	30						

Data shown in parenthesis are test/reference ratios based on geometric means.

Table 2. Mean Recovery Data From Five Actuations In Cascade Impaction Study (N=30).									
		Test			Reference				
Sector	Grp	Mean	%CV	%/Grp	Mean	%CV	%/Grp	T/R	*P*
BEGIN	1	5188.83	4.6	99.3	5141.90	10.8	99.2	1.01 (1.01)	*0.34085*
	2	5.21	29.6	0.1	6.84	103.6	0.1	0.76 (0.89)	*0.10733*
	3	33.57	33.7	0.6	34.56	38.4	0.7	0.97 (1.01)	*0.37782*
END	1	4952.02	6.2	99.3	4979.39	4.7	99.2	0.99 (0.99)	*0.34337*
	2	4.01	34.1	0.1	4.59	42.4	0.1	0.87 (0.90)	*0.11064*
	3	30.43	40.0	0.6	33.64	39.2	0.7	0.90 (0.90)	*0.14931*

Data shown in parenthesis are test/reference ratios that are based on geometric means.
Grp = Group.

Table 3. Spray Pattern Testing Data: Calculated from the Pattern Center (N=30)						
Distance (cm)	**Stage**	**Product**	**Statistic**	**Dmax (mm)**	**Dmin (mm)**	**Ovality Ratio**
3	Begin	Test	Mean	37.510	32.859 **(32.711)**	1.147 **(1.143)**
			%CV	7.8	9.1	8.4
		Reference	Mean	35.904	31.278	1.159
			%CV	10.0	8.6	16.6
			T/R	1.045 (1.047)	1.051 (1.050)	0.990 (0.997)
			P	*0.02393*	*0.00575*	*0.38019*
	End	Test	Mean	38.414	34.386	1.121
			%CV	8.3	10.2	5.8
		Reference	Mean	36.345	32.200	1.136
			%CV	9.8	8.6	13.6
			T/R	1.057 (1.058)	1.068 (1.066)	0.987 (0.992)
			P	*0.00452*	*0.00241*	*0.29922*
4	Begin	Test	Mean	45.660	37.728	1.214
			%CV	9.3	8.9	8.8
		Reference	Mean	41.304	34.162	1.223
			%CV	12.9	10.2	19.5
			T/R	1.105 (1.110)	1.104 (1.106)	0.993 (1.003)
			P	*0.00055*	*0.00011*	*0.42132*
	End	Test	Mean	46.282	38.705	1.199
			%CV	8.9	8.5	8.1
		Reference	Mean	42.336	35.455	1.212
			%CV	12.1	11.3	20.2
			T/R	1.093 (1.097)	1.092 (1.095)	0.990 (1.001)
			P	*0.00066*	*0.00121*	*0.39316*
5	Begin	Test	Mean	54.670	43.265	1.266
			%CV	11.2	7.3	10.6
		Reference	Mean	48.037	37.455	1.305
			%CV	15.3	14.6	21.9
			T/R	1.138 (1.145)	1.155 (1.164)	0.970 (0.983)
			P	*0.00008*	*0.00000*	*0.22806*
	End	Test	Mean	55.927	44.913	1.249
			%CV	11.1	10.1	9.1
		Reference	Mean	49.141	39.039	1.284
			%CV	13.8	11.9	23.6
			T/R	1.138 (1.141)	1.150 (1.153)	0.973 (0.990)
			P	*0.00011*	*0.00003*	*0.27083*

Data shown in parenthesis are test/reference ratios that are based on geometric means.

Table 4. Droplet Size Distribution Determined By [redacted] At Beginning, Middle And End Stages (N=30).

Stage of Unit Life	Distance (cm)	Delay Time (Sec)	D50						SPAN					
			Test		Reference				Test		Reference			
			Mean (µm)	%CV	Mean	%CV	T/R	*P*	Mean	%CV	Mean	%CV	T/R	*p*
Begin	1	15	53.08	15.2	57.28	12.9	0.93(0.92)	0.026	1.64	6.0	1.72	9.9	0.95(0.95)	0.012
	1	45	59.81	12.0	64.91	18.6	0.92(0.93)	0.025	1.53	5.8	1.63	9.2	0.94(0.94)	0.004
	1	75	72.95	39.3	70.61	27.3	1.03(1.01)	0.364	1.54	9.7	1.67	18.2	0.92(0.93)	0.021
	3	15	45.24	15.3	46.71	14.5	0.97(0.97)	0.209	1.65	6.3	1.71	25.1	0.96(0.98)	0.232
	3	45	50.33	13.2	54.42	13.4	0.92(0.92)	0.016	1.60	4.4	1.62	24.1	0.98(1.00)	0.348
	3	75	66.02	45.4	63.92	28.4	1.03(1.00)	0.385	1.57	6.8	1.58	9.1	0.99(0.99)	0.325
	5	15	40.76	12.6	43.92	9.9	0.93(0.93)	0.003	1.45	11.1	1.44	14.4	1.00(1.01)	0.469
	5	45	46.35	12.9	51.95	11.2	0.89(0.89)	0.000	1.37	10.3	1.36	11.8	1.01(1.01)	0.368
	5	75	58.20	43.8	64.40	42.4	0.90(0.90)	0.207	1.46	12.4	1.45	22.2	1.01(1.02)	0.447
Mean Begin Stage			**54.75**	**19.1**	**57.57**	**15.7**	**0.95**	**--**	**1.53**	**6.1**	**1.58**	**8.3**	**0.97**	**--**
Middle	1	15	51.57	13.5	57.04	15.5	0.90(0.90)	0.009	1.62	4.8	1.94	47.8	0.83(0.88)	0.033
	1	45	57.93	13.2	61.94	12.3	0.94(0.93)	0.032	1.53	4.4	1.71	19.2	0.90(0.91)	0.004
	1	75	62.08	11.7	65.14	12.9	0.95(0.95)	0.073	1.53	3.6	1.86	45.7	0.82(0.87)	0.023
	3	15	42.14	14.6	45.83	14.4	0.92(0.92)	0.004	1.66	6.1	1.64	14.8	1.01(1.01)	0.408
	3	45	49.62	17.0	52.47	13.6	0.95(0.94)	0.049	1.56	6.3	1.55	7.2	1.01(1.01)	0.231
	3	75	56.47	19.5	57.22	13.2	0.99(0.98)	0.370	1.56	6.4	1.50	7.5	1.04(1.04)	0.011
	5	15	41.76	11.2	44.51	14.3	0.94(0.94)	0.033	1.49	10.3	1.49	23.0	1.01(1.02)	0.453
	5	45	48.27	11.2	51.80	11.9	0.93(0.93)	0.007	1.40	11.1	1.38	24.3	1.01(1.03)	0.408
	5	75	53.10	27.8	55.81	11.8	0.95(0.93)	0.163	1.43	15.0	1.42	21.2	1.01(1.01)	0.419
Mean Middle Stage			**51.44**	**13.3**	**54.64**	**12.5**	**0.94**	**--**	**1.53**	**5.4**	**1.61**	**12.1**	**0.95**	**--**
End	1	15	52.49	10.9	58.10	16.1	0.90(0.91)	0.002	1.63	5.5	2.10	52.4	0.78(0.84)	0.013
	1	45	58.44	11.1	63.75	15.9	0.92(0.92)	0.009	1.56	5.6	1.76	29.9	0.89(0.91)	0.022
	1	75	68.01	57.5	67.22	17.1	1.01(0.96)	0.457	1.55	7.4	1.72	27.7	0.90(0.92)	0.029
	3	15	44.63	15.0	47.32	18.4	0.94(0.95)	0.096	1.64	7.1	1.75	17.1	0.94(0.94)	0.025
	3	45	50.79	14.8	54.01	16.7	0.94(0.94)	0.076	1.56	7.1	1.62	12.4	0.97(0.97)	0.094
	3	75	58.35	25.3	58.98	16.6	0.99(0.98)	0.428	1.59	9.4	1.58	10.6	1.01(1.01)	0.360
	5	15	41.41	11.5	42.14	11.5	0.98(0.98)	0.291	1.53	7.1	1.56	17.0	0.98(0.99)	0.271
	5	45	48.19	13.6	50.05	12.5	0.96(0.96)	0.155	1.42	6.2	1.48	23.4	0.96(0.98)	0.221
	5	75	57.77	51.2	53.84	11.4	1.07(1.01)	0.239	1.45	11.5	1.50	25.7	0.97(0.98)	0.291
Mean End Stage			**53.34**	**15.4**	**55.05**	**14.4**	**0.97**	**--**	**1.55**	**4.7**	**1.67**	**11.4**	**0.93**	**--**

Data shown in parenthesis are test/reference ratios that are based on geometric means.

Table 5. Plume Geometry Data (N=30)						
Time (msec)	**View**	**Product**	**Statistic**	**Length (cm)**	**Width (cm)**	**Angle (°)**
20	Front	Test	Mean	15.59	11.26	60.9
			%CV	9.9	13.9	10.9
		Reference	Mean	15.55	10.49	58.5
			%CV	14.3	13.5	10.3
			T/R	1.003 (1.008)	1.074 (1.073)	1.041 (1.040)
			p	*0.470*	*0.024*	*0.072*
	Side	Test	Mean	15.33	11.55	61.5
			%CV	10.4	12.9	10.0
		Reference	Mean	15.557	10.21	58.5
			%CV	13.7	13.4	7.2
			T/R	0.985 (0.989)	1.131 (1.132)	1.051 (1.048)
			p	*0.332*	*0.002*	*0.020*
75	Front	Test	Mean	28.18	16.49	54.6
			%CV	7.2	14.4	13.4
		Reference	Mean	28.63	15.66	50.7
			%CV	7.1	14.0	14.6
			T/R	0.984 (0.984)	1.053 (1.052)	1.076 (1.079)
			p	*0.208*	*0.095*	*0.026*
	Side	Test	Mean	28.19	16.75	54.0
			%CV	7.1	12.6	13.4
		Reference	Mean	28.86	15.32	51.2
			%CV	8.6	12.3	15.5
			T/R	0.977 (0.978)	1.094 (1.093)	1.056 (1.060)
			P	*0.146*	*0.009*	*0.078*
150	Front	Test	Mean	37.33	18.56	54.3
			%CV	8.0	12.9	13.8
		Reference	Mean	38.58	17.24	49.8
			%CV	4.5	13.3	11.7
			T/R	0.967 (0.965)	1.077 (1.078)	1.090 (1.087)
			P	*0.027*	*0.026*	*0.013*
	Side	Test	Mean	36.97	18.88	54.6
			%CV	7.1	11.7	13.0
		Reference	Mean	38.56	17.10	50.3
			%CV	5.0	10.0	9.3
			T/R	0.959 (0.958)	1.105 (1.102)	1.085 (1.081)
			P	*0.006*	*0.004*	*0.009*

Data shown in parenthesis are test/reference ratios that are based on geometric means.

2. Review of Amendment to Original March 24, 2000 Submission

2.1 Deficiency 1:
Please report expiration dates for the three lots of reference product.
Firm's Response:
The expiration dates for the three reference products (Stadol NS® Nasal Spray) are as follows: Lot 9FI0028, 5/31/01; Lot 9F13540, 5/31/01; Lot 9F15910, 6/30/01.
Review's Comment:
The firm's response is acceptable.

2.2 Deficiency 2:
Please submit representative (at least 20%) computer printout sheets for the [redacted] analysis.
Firm's Response:
Representative (20%) computer printouts (data plots) for the [redacted] analysis were submitted.
Review's Comment:
The firm's response is acceptable.

2.3 Deficiency 3:
The quantification for the priming/re-priming and tail-off testing was accomplished by taking individual actuation weights. In these tests, please base your measurements of drug per actuation on a validated [redacted] assay and resubmit the raw data to the Agency for evaluation.
Firm's Response:

Priming/re-priming
Actuations 6 through 8, 13, 14 and 21 were collected for [redacted] assay. The results confirmed that the two formulations are equivalent with respect to priming/re-priming when the amount of drug in each actuation is directly measured by [redacted] (Table 6).

Table 6. Amended Priming/Re-priming Data (mg/Spray) –

	Test			Reference			
Spray #	Mean	%CV	N	Mean	%CV	N	T/R
6	1.032	4.6	31	1.025	4.4	31	1.007
7	1.045	4.0	31	1.035	4.8	31	1.010
8	1.058	4.5	31	1.056	4.9	31	1.002
13	1.073	2.6	31	1.065	2.1	31	1.008
14	1.053	5.2	31	1.067	2.0	31	0.988
21	1.067	3.8	31	1.075	1.5	31	0.993

Tail-off
Actuations 24, 27, 29 and 31 were collected for [redacted] assay. The results presented in this report comparing Roxane's Butorphanol Nasal Spray and Stadol NS have confirmed that the two formulations are equivalent with respect to tailing-off when the amount of drug in each actuation is directly measured by [redacted] (Table 7).

Table 7. Amended Tail Off Data (mg/spray) – HPLC							
	Test			Reference			
Spray #	Mean	%CV	N	Mean	%CV	N	T/R
24	0.949	16.6	31	1.068	2.9	31	0.888
27	0.137	109.1	21	0.697	22.2	31	0.197
29	0	-	0	0.194	45.3	25	0
31	0	-	0	0.076	-	1	0

Reviewer's Comment:
The priming/re-priming and tail-off testing based on measurements of drug per actuation using the chromatographic assay is acceptable.

2.4 Deficiency 4:

[redacted]

Firm's Response:

[redacted]

Review's Comment:
The firm's response is acceptable.

2.5 Deficiency 5:

[redacted]

Review's Comment:
The firm's response is acceptable.

2.6 Deficiency 6:
You submitted only a hard copy of the raw plume data. In future applications on this dosage form you should submit diskettes of the raw plume data in Microsoft Excel.
Firm's Response:
The firm acknowledged that in future applications on this dosage form, it will submit diskette copies of the raw plume data in Microsoft Excel.
Review's Comment:
The firm's response is acceptable.

3. Recommendation:

The formulation of the test product is Q1 and Q2 the same as that of the reference product. The *in vitro* testing conducted by Roxane Laboratories comparing its butorphanol tartrate nasal spray (10 mg/mL) and the reference product (Stadol nasal spray, 10 mg/mL) has been found acceptable to the Division of Bioequivalence. In terms of dose delivered per actuation and the size, shape and droplet size distribution of the spray, the test product's performance is similar to that of the reference product. Therefore, the Division of Bioequivalence deems the test product to be equivalent to the reference product in dose delivery and performance of the delivery device.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

/S/

RD INITIALED YCHuang
FT INITIALED YCHuang _____ Date 5/21/01

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Concur._____ Date 5/22/2001
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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Attachment 1

Non-Profile Bioequivalence

Test: Spray Pattern II
Summary Table

Distance (cm)	BE Variable	Geometric Mean		Geometric Mean Ratio (%)	Standard Deviation		Upper Confidence Bound †
		Test	Reference		Reference	T/R Ratio	
3	D_{max}	37.84	35.96	105.24	0.098	0.836	-0.008
	D_{min}	33.45	31.61	105.81	0.091	1.141	-0.001
	Ovality Ratio	1.13	1.14	99.46	0.127	0.547	-0.023
4	D_{max}	45.78	41.50	110.32	0.126	0.746	-0.006
	D_{min}	38.07	34.59	110.06	0.115	0.774	-0.003
	Ovality Ratio	1.20	1.20	100.24	0.163	0.509	-0.039
5	D_{max}	54.97	48.08	114.32	0.147	0.766	-0.002
	D_{min}	43.91	37.89	115.87	0.140	0.659	**0.001 (-0.017)**
	Ovality Ratio	1.25	1.27	98.66	0.192	0.498	-0.054

† A negative upper confidence bound means the test product passes this bioequivalence test. These 95% upper confidence bounds use the regulatory constants suggested in the draft guidance, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", June 1999; that is, average BE criterion (GMR) of 90/111, $\varepsilon = 0$, and $\sigma_0 = 0.1$. If the bioequivalence test fails using these constants, then the alternate values suggested in the guidance (i.e., $\varepsilon = 0.01$ and the other two unchanged) are reported in parentheses.

Dataset: aspraprtn.xls
3/7/2001

ANDA 75-824

APPEARS THIS WAY
ON ORIGINAL

dm=' 3 / Dmax'

Obs	Sigma T0	epsilon	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
1	0.1	0.00	1.11	1.09	37.8	36.0	105.24	0.08	0.10	0.84	-0.0061	-0.0076	-0.007622
2	0.1	0.00	1.25	4.98	37.8	36.0	105.24	0.08	0.10	0.84	-0.0379	-0.0465	-0.046524
3	0.2	0.00	1.11	0.27	37.8	36.0	105.24	0.08	0.10	0.84	0.0009	-0.0076	-0.007622
4	0.2	0.00	1.25	1.24	37.8	36.0	105.24	0.08	0.10	0.84	-0.0074	-0.0465	-0.046524
5	0.1	0.01	1.11	2.09	37.8	36.0	105.24	0.08	0.10	0.84	-0.0144	-0.0176	-0.017622
6	0.1	0.01	1.25	5.98	37.8	36.0	105.24	0.08	0.10	0.84	-0.0459	-0.0565	-0.056524
7	0.2	0.01	1.11	0.52	37.8	36.0	105.24	0.08	0.10	0.84	-0.0013	-0.0176	-0.017622
8	0.2	0.01	1.25	1.49	37.8	36.0	105.24	0.08	0.10	0.84	-0.0095	-0.0565	-0.056524
9	0.1	0.03	1.11	4.09	37.8	36.0	105.24	0.08	0.10	0.84	-0.0307	-0.0376	-0.037622
10	0.1	0.03	1.25	7.98	37.8	36.0	105.24	0.08	0.10	0.84	-0.0620	-0.0765	-0.076524
11	0.2	0.03	1.11	1.02	37.8	36.0	105.24	0.08	0.10	0.84	-0.0055	-0.0376	-0.037622
12	0.2	0.03	1.25	1.99	37.8	36.0	105.24	0.08	0.10	0.84	-0.0136	-0.0765	-0.076524
13	0.1	0.05	1.11	6.09	37.8	36.0	105.24	0.08	0.10	0.84	-0.0468	-0.0576	-0.057622
14	0.1	0.05	1.25	9.98	37.8	36.0	105.24	0.08	0.10	0.84	-0.0780	-0.0965	-0.096524
15	0.2	0.05	1.11	1.52	37.8	36.0	105.24	0.08	0.10	0.84	-0.0097	-0.0576	-0.057622
16	0.2	0.05	1.25	2.49	37.8	36.0	105.24	0.08	0.10	0.84	-0.0177	-0.0965	-0.096524

dm=' 3 / Dmin'

Obs	Sigma T0	epsilon	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
17	0.1	0.00	1.11	1.09	33.5	31.6	105.81	0.10	0.09	1.14	0.0017	-0.0009	-0.000892
18	0.1	0.00	1.25	4.98	33.5	31.6	105.81	0.10	0.09	1.14	-0.0260	-0.0398	-0.039794
19	0.2	0.00	1.11	0.27	33.5	31.6	105.81	0.10	0.09	1.14	0.0079	-0.0009	-0.000892
20	0.2	0.00	1.25	1.24	33.5	31.6	105.81	0.10	0.09	1.14	0.0006	-0.0398	-0.039794
21	0.1	0.01	1.11	2.09	33.5	31.6	105.81	0.10	0.09	1.14	-0.0056	-0.0109	-0.010892
22	0.1	0.01	1.25	5.98	33.5	31.6	105.81	0.10	0.09	1.14	-0.0329	-0.0498	-0.049794
23	0.2	0.01	1.11	0.52	33.5	31.6	105.81	0.10	0.09	1.14	0.0060	-0.0109	-0.010892
24	0.2	0.01	1.25	1.49	33.5	31.6	105.81	0.10	0.09	1.14	-0.0013	-0.0498	-0.049794
25	0.1	0.03	1.11	4.09	33.5	31.6	105.81	0.10	0.09	1.14	-0.0198	-0.0309	-0.030892
26	0.1	0.03	1.25	7.98	33.5	31.6	105.81	0.10	0.09	1.14	-0.0468	-0.0698	-0.069794
27	0.2	0.03	1.11	1.02	33.5	31.6	105.81	0.10	0.09	1.14	0.0022	-0.0309	-0.030892
28	0.2	0.03	1.25	1.99	33.5	31.6	105.81	0.10	0.09	1.14	-0.0049	-0.0698	-0.069794
29	0.1	0.05	1.11	6.09	33.5	31.6	105.81	0.10	0.09	1.14	-0.0337	-0.0509	-0.050892
30	0.1	0.05	1.25	9.98	33.5	31.6	105.81	0.10	0.09	1.14	-0.0606	-0.0898	-0.089794
31	0.2	0.05	1.11	1.52	33.5	31.6	105.81	0.10	0.09	1.14	-0.0015	-0.0509	-0.050892
32	0.2	0.05	1.25	2.49	33.5	31.6	105.81	0.10	0.09	1.14	-0.0085	-0.0898	-0.089794

dm=' 3 / Ovality Ratio'

Obs	Sigma TG	epsilon	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
33	0.1	0.00	1.11	1.09	1.13	1.14	99.46	0.07	0.13	0.55	-0.0229	-0.0191	-0.02291
34	0.1	0.00	1.25	4.98	1.13	1.14	99.46	0.07	0.13	0.55	-0.0750	-0.0580	-0.07504
35	0.2	0.00	1.11	0.27	1.13	1.14	99.46	0.07	0.13	0.55	-0.0119	-0.0191	-0.01908
36	0.2	0.00	1.25	1.24	1.13	1.14	99.46	0.07	0.13	0.55	-0.0250	-0.0580	-0.05798
37	0.1	0.01	1.11	2.09	1.13	1.14	99.46	0.07	0.13	0.55	-0.0363	-0.0291	-0.03634
38	0.1	0.01	1.25	5.98	1.13	1.14	99.46	0.07	0.13	0.55	-0.0884	-0.0680	-0.08842
39	0.2	0.01	1.11	0.52	1.13	1.14	99.46	0.07	0.13	0.55	-0.0153	-0.0291	-0.02908
40	0.2	0.01	1.25	1.49	1.13	1.14	99.46	0.07	0.13	0.55	-0.0284	-0.0680	-0.06798
41	0.1	0.03	1.11	4.09	1.13	1.14	99.46	0.07	0.13	0.55	-0.0631	-0.0491	-0.06313
42	0.1	0.03	1.25	7.98	1.13	1.14	99.46	0.07	0.13	0.55	-0.1152	-0.0880	-0.11518
43	0.2	0.03	1.11	1.02	1.13	1.14	99.46	0.07	0.13	0.55	-0.0220	-0.0491	-0.04908
44	0.2	0.03	1.25	1.99	1.13	1.14	99.46	0.07	0.13	0.55	-0.0351	-0.0880	-0.08798
45	0.1	0.05	1.11	6.09	1.13	1.14	99.46	0.07	0.13	0.55	-0.0899	-0.0691	-0.08989
46	0.1	0.05	1.25	9.98	1.13	1.14	99.46	0.07	0.13	0.55	-0.1419	-0.1080	-0.14193
47	0.2	0.05	1.11	1.52	1.13	1.14	99.46	0.07	0.13	0.55	-0.0287	-0.0691	-0.06908
48	0.2	0.05	1.25	2.49	1.13	1.14	99.46	0.07	0.13	0.55	-0.0418	-0.1080	-0.10798

dm=' 4 / Dmax'

Obs	Sigma T0	epsilon	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
49	0.1	0.00	1.11	1.09	45.8	41.5	110.32	0.09	0.13	0.75	-0.0062	-0.0015	-0.00617
50	0.1	0.00	1.25	4.98	45.8	41.5	110.32	0.09	0.13	0.75	-0.0587	-0.0404	-0.05873
51	0.2	0.00	1.11	0.27	45.8	41.5	110.32	0.09	0.13	0.75	0.0054	-0.0015	-0.00147
52	0.2	0.00	1.25	1.24	45.8	41.5	110.32	0.09	0.13	0.75	-0.0083	-0.0404	-0.04038
53	0.1	0.01	1.11	2.09	45.8	41.5	110.32	0.09	0.13	0.75	-0.0200	-0.0115	-0.01996
54	0.1	0.01	1.25	5.98	45.8	41.5	110.32	0.09	0.13	0.75	-0.0720	-0.0504	-0.07198
55	0.2	0.01	1.11	0.52	45.8	41.5	110.32	0.09	0.13	0.75	0.0018	-0.0115	-0.01147
56	0.2	0.01	1.25	1.49	45.8	41.5	110.32	0.09	0.13	0.75	-0.0118	-0.0504	-0.05038
57	0.1	0.03	1.11	4.09	45.8	41.5	110.32	0.09	0.13	0.75	-0.0469	-0.0315	-0.04668
58	0.1	0.03	1.25	7.98	45.8	41.5	110.32	0.09	0.13	0.75	-0.0984	-0.0704	-0.09840
59	0.2	0.03	1.11	1.02	45.8	41.5	110.32	0.09	0.13	0.75	-0.0052	-0.0315	-0.03147
60	0.2	0.03	1.25	1.99	45.8	41.5	110.32	0.09	0.13	0.75	-0.0187	-0.0704	-0.07038
61	0.1	0.05	1.11	6.09	45.8	41.5	110.32	0.09	0.13	0.75	-0.0734	-0.0515	-0.07344
62	0.1	0.05	1.25	9.98	45.8	41.5	110.32	0.09	0.13	0.75	-0.1247	-0.0904	-0.12474
63	0.2	0.05	1.11	1.52	45.8	41.5	110.32	0.09	0.13	0.75	-0.0122	-0.0515	-0.05147
64	0.2	0.05	1.25	2.49	45.8	41.5	110.32	0.09	0.13	0.75	-0.0255	-0.0904	-0.09038

dm=' 4 / Dmin'

Obs	Sigma T0	epsilon	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
65	0.1	0.00	1.11	1.09	38.1	34.6	110.06	0.09	0.11	0.77	-0.0031	-0.0010	-0.00314
66	0.1	0.00	1.25	4.98	38.1	34.6	110.06	0.09	0.11	0.77	-0.0471	-0.0399	-0.04711
67	0.2	0.00	1.11	0.27	38.1	34.6	110.06	0.09	0.11	0.77	0.0066	-0.0010	-0.00098
68	0.2	0.00	1.25	1.24	38.1	34.6	110.06	0.09	0.11	0.77	-0.0050	-0.0399	-0.03987
69	0.1	0.01	1.11	2.09	38.1	34.6	110.06	0.09	0.11	0.77	-0.0147	-0.0110	-0.01469
70	0.1	0.01	1.25	5.98	38.1	34.6	110.06	0.09	0.11	0.77	-0.0582	-0.0499	-0.05818
71	0.2	0.01	1.11	0.52	38.1	34.6	110.06	0.09	0.11	0.77	0.0036	-0.0110	-0.01096
72	0.2	0.01	1.25	1.49	38.1	34.6	110.06	0.09	0.11	0.77	-0.0079	-0.0499	-0.04987
73	0.1	0.03	1.11	4.09	38.1	34.6	110.06	0.09	0.11	0.77	-0.0372	-0.0310	-0.03721
74	0.1	0.03	1.25	7.98	38.1	34.6	110.06	0.09	0.11	0.77	-0.0802	-0.0699	-0.08022
75	0.2	0.03	1.11	1.02	38.1	34.6	110.06	0.09	0.11	0.77	-0.0024	-0.0310	-0.03096
76	0.2	0.03	1.25	1.99	38.1	34.6	110.06	0.09	0.11	0.77	-0.0136	-0.0699	-0.06987
77	0.1	0.05	1.11	6.09	38.1	34.6	110.06	0.09	0.11	0.77	-0.0594	-0.0510	-0.05939
78	0.1	0.05	1.25	9.98	38.1	34.6	110.06	0.09	0.11	0.77	-0.1022	-0.0899	-0.10220
79	0.2	0.05	1.11	1.52	38.1	34.6	110.06	0.09	0.11	0.77	-0.0082	-0.0510	-0.05096
80	0.2	0.05	1.25	2.49	38.1	34.6	110.06	0.09	0.11	0.77	-0.0193	-0.0899	-0.08987

Attachment II
Droplet Size Distribution
Summary Table

			Geometric		Geometric	Standard		Upper
BE	Distance	Delay	Mean		Mean	Deviation		Confidence
Measure	(cm)	(msec)	Test	Reference	Ratio (%)	Reference	T/R Ratio	Bound †
D50	1	15	51.94	56.93	91.23	0.135	0.978	-0.005
		45	58.30	62.89	92.70	0.138	0.895	-0.012
		75	64.87	66.67	97.29	0.165	1.524	0.020 (-0.004)
	3	15	43.52	46.11	94.38	0.147	1.037	-0.011
		45	49.70	53.11	93.57	0.138	1.098	-0.005
		75	58.05	58.97	98.43	0.182	1.394	0.010 (-0.020)
	5	15	41.05	43.23	94.95	0.117	0.992	-0.007
		45	47.26	50.92	92.80	0.116	1.060	-0.001
		75	53.60	56.61	94.68	0.198	1.414	0.017 (-0.019)
Span	1	15	1.63	1.83	89.06	0.273	0.196	-0.119
		45	1.54	1.67	91.99	0.157	0.341	-0.034
		75	1.54	1.69	90.65	0.221	0.319	-0.071
	3	15	1.64	1.68	97.86	0.146	0.455	-0.032
		45	1.57	1.58	99.42	0.121	0.520	-0.022
		75	1.57	1.5 5	101.35	0.088	0.865	-0.011
	5	15	1.48	1.48	100.46	0.160	0.611	-0.036
		45	1.39	1.38	100.49	0.158	0.597	-0.036
		75	1.44	1.43	100.59	0.177	0.717	-0.038

† 95% upper confidence bound uses the regulatory constants suggested in the draft guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", June 1999

Attachment II (cont)

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metric=D50 distance=1 delay=15

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
1	0.1	0.00	0.1	1.11	1.089	51.94	56.93	91.225	0.132	0.135	0.978	-0.0050	0.0022	-0.00505
2	0.1	0.00	0.1	1.25	4.979	51.94	56.93	91.225	0.132	0.135	0.978	-0.0673	-0.0367	-0.06730
3	0.2	0.00	0.2	1.11	0.272	51.94	56.93	91.225	0.132	0.135	0.978	0.0085	0.0022	0.00222
4	0.2	0.00	0.2	1.25	1.245	51.94	56.93	91.225	0.132	0.135	0.978	-0.0076	-0.0367	-0.03668
5	0.1	0.01	0.1	1.11	2.089	51.94	56.93	91.225	0.132	0.135	0.978	-0.0213	-0.0078	-0.02127
6	0.1	0.01	0.1	1.25	5.979	51.94	56.93	91.225	0.132	0.135	0.978	-0.0831	-0.0467	-0.08311
7	0.2	0.01	0.2	1.11	0.522	51.94	56.93	91.225	0.132	0.135	0.978	0.0043	-0.0078	-0.00778
8	0.2	0.01	0.2	1.25	1.495	51.94	56.93	91.225	0.132	0.135	0.978	-0.0117	-0.0467	-0.04668
9	0.1	0.03	0.1	1.11	4.089	51.94	56.93	91.225	0.132	0.135	0.978	-0.0532	-0.0278	-0.05319
10	0.1	0.03	0.1	1.25	7.979	51.94	56.93	91.225	0.132	0.135	0.978	-0.1147	-0.0667	-0.11466
11	0.2	0.03	0.2	1.11	1.022	51.94	56.93	91.225	0.132	0.135	0.978	-0.0040	-0.0278	-0.02778
12	0.2	0.03	0.2	1.25	1.995	51.94	56.93	91.225	0.132	0.135	0.978	-0.0197	-0.0667	-0.06668
13	0.1	0.05	0.1	1.11	6.089	51.94	56.93	91.225	0.132	0.135	0.978	-0.0848	-0.0478	-0.08484
14	0.1	0.05	0.1	1.25	9.979	51.94	56.93	91.225	0.132	0.135	0.978	-0.1462	-0.0867	-0.14616
15	0.2	0.05	0.2	1.11	1.522	51.94	56.93	91.225	0.132	0.135	0.978	-0.0121	-0.0478	-0.04778
16	0.2	0.05	0.2	1.25	2.495	51.94	56.93	91.225	0.132	0.135	0.978	-0.0278	-0.0867	-0.08668

metric=D50 distance=1 delay=45

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
17	0.1	0.00	0.1	1.11	1.089	58.30	62.89	92.699	0.123	0.138	0.895	-0.0119	-0.0040	-0.011892
18	0.1	0.00	0.1	1.25	4.979	58.30	62.89	92.699	0.123	0.138	0.895	-0.0767	-0.0429	-0.076702
19	0.2	0.00	0.2	1.11	0.272	58.30	62.89	92.699	0.123	0.138	0.895	0.0021	-0.0040	-0.003978
20	0.2	0.00	0.2	1.25	1.245	58.30	62.89	92.699	0.123	0.138	0.895	-0.0145	-0.0429	-0.042880
21	0.1	0.01	0.1	1.11	2.089	58.30	62.89	92.699	0.123	0.138	0.895	-0.0287	-0.0140	-0.028732
22	0.1	0.01	0.1	1.25	5.979	58.30	62.89	92.699	0.123	0.138	0.895	-0.0932	-0.0529	-0.093211
23	0.2	0.01	0.2	1.11	0.522	58.30	62.89	92.699	0.123	0.138	0.895	-0.0022	-0.0140	-0.013978

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Attachment II (cont)

metric=D50 distance=1 delay=45 (continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
24	0.2	0.01	0.2	1.25	1.495	58.30	62.89	92.699	0.123	0.138	0.895	-0.0188	-0.0529	-0.05288
25	0.1	0.03	0.1	1.11	4.089	58.30	62.89	92.699	0.123	0.138	0.895	-0.0620	-0.0340	-0.06198
26	0.1	0.03	0.1	1.25	7.979	58.30	62.89	92.699	0.123	0.138	0.895	-0.1262	-0.0729	-0.12618
27	0.2	0.03	0.2	1.11	1.022	58.30	62.89	92.699	0.123	0.138	0.895	-0.0108	-0.0340	-0.03398
28	0.2	0.03	0.2	1.25	1.995	58.30	62.89	92.699	0.123	0.138	0.895	-0.0272	-0.0729	-0.07288
29	0.1	0.05	0.1	1.11	6.089	58.30	62.89	92.699	0.123	0.138	0.895	-0.0950	-0.0540	-0.09502
30	0.1	0.05	0.1	1.25	9.979	58.30	62.89	92.699	0.123	0.138	0.895	-0.1591	-0.0929	-0.15910
31	0.2	0.05	0.2	1.11	1.522	58.30	62.89	92.699	0.123	0.138	0.895	-0.0192	-0.0540	-0.05398
32	0.2	0.05	0.2	1.25	2.495	58.30	62.89	92.699	0.123	0.138	0.895	-0.0355	-0.0929	-0.09288

metric=D50 distance=1 delay=75

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
33	0.1	0.00	0.1	1.11	1.089	64.87	66.67	97.292	0.251	0.165	1.524	0.0202	0.0369	0.02024
34	0.1	0.00	0.1	1.25	4.979	64.87	66.67	97.292	0.251	0.165	1.524	-0.0736	-0.0020	-0.07357
35	0.2	0.00	0.2	1.11	0.272	64.87	66.67	97.292	0.251	0.165	1.524	0.0408	0.0369	0.03693
36	0.2	0.00	0.2	1.25	1.245	64.87	66.67	97.292	0.251	0.165	1.524	0.0164	-0.0020	-0.00198
37	0.1	0.01	0.1	1.11	2.089	64.87	66.67	97.292	0.251	0.165	1.524	-0.0043	0.0269	-0.00434
38	0.1	0.01	0.1	1.25	5.979	64.87	66.67	97.292	0.251	0.165	1.524	-0.0972	-0.0120	-0.09723
39	0.2	0.01	0.2	1.11	0.522	64.87	66.67	97.292	0.251	0.165	1.524	0.0345	0.0269	0.02693
40	0.2	0.01	0.2	1.25	1.495	64.87	66.67	97.292	0.251	0.165	1.524	0.0102	-0.0120	-0.01198
41	0.1	0.03	0.1	1.11	4.089	64.87	66.67	97.292	0.251	0.165	1.524	-0.0524	0.0069	-0.05241
42	0.1	0.03	0.1	1.25	7.979	64.87	66.67	97.292	0.251	0.165	1.524	-0.1444	-0.0320	-0.14437
43	0.2	0.03	0.2	1.11	1.022	64.87	66.67	97.292	0.251	0.165	1.524	0.0219	0.0069	0.00693
44	0.2	0.03	0.2	1.25	1.995	64.87	66.67	97.292	0.251	0.165	1.524	-0.0020	-0.0320	-0.03198
45	0.1	0.05	0.1	1.11	6.089	64.87	66.67	97.292	0.251	0.165	1.524	-0.0998	-0.0131	-0.09982

Attachment II (cont)

metric=D50 distance=1 delay=75 (continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
46	0.1	0.05	0.1	1.25	9.979	64.87	66.67	97.292	0.251	0.165	1.524	-0.1914	-0.0520	-0.19136
47	0.2	0.05	0.2	1.11	1.522	64.87	66.67	97.292	0.251	0.165	1.524	0.0095	-0.0131	-0.01307
48	0.2	0.05	0.2	1.25	2.495	64.87	66.67	97.292	0.251	0.165	1.524	-0.0142	-0.0520	-0.05198

metric=D50 distance=3 delay=15

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
49	0.1	0.00	0.1	1.11	1.089	43.52	46.11	94.383	0.152	0.147	1.037	-0.0110	-0.0003	-0.01096
50	0.1	0.00	0.1	1.25	4.979	43.52	46.11	94.383	0.152	0.147	1.037	-0.0851	-0.0392	-0.08514
51	0.2	0.00	0.2	1.11	0.272	43.52	46.11	94.383	0.152	0.147	1.037	0.0051	-0.0003	-0.00033
52	0.2	0.00	0.2	1.25	1.245	43.52	46.11	94.383	0.152	0.147	1.037	-0.0140	-0.0392	-0.03924
53	0.1	0.01	0.1	1.11	2.089	43.52	46.11	94.383	0.152	0.147	1.037	-0.0302	-0.0103	-0.03024
54	0.1	0.01	0.1	1.25	5.979	43.52	46.11	94.383	0.152	0.147	1.037	-0.1040	-0.0492	-0.10403
55	0.2	0.01	0.2	1.11	0.522	43.52	46.11	94.383	0.152	0.147	1.037	0.0001	-0.0103	-0.01033
56	0.2	0.01	0.2	1.25	1.495	43.52	46.11	94.383	0.152	0.147	1.037	-0.0188	-0.0492	-0.04924
57	0.1	0.03	0.1	1.11	4.089	43.52	46.11	94.383	0.152	0.147	1.037	-0.0683	-0.0303	-0.06829
58	0.1	0.03	0.1	1.25	7.979	43.52	46.11	94.383	0.152	0.147	1.037	-0.1417	-0.0692	-0.14175
59	0.2	0.03	0.2	1.11	1.022	43.52	46.11	94.383	0.152	0.147	1.037	-0.0097	-0.0303	-0.03033
60	0.2	0.03	0.2	1.25	1.995	43.52	46.11	94.383	0.152	0.147	1.037	-0.0284	-0.0692	-0.06924
61	0.1	0.05	0.1	1.11	6.089	43.52	46.11	94.383	0.152	0.147	1.037	-0.1061	-0.0503	-0.10610
62	0.1	0.05	0.1	1.25	9.979	43.52	46.11	94.383	0.152	0.147	1.037	-0.1794	-0.0892	-0.17942
63	0.2	0.05	0.2	1.11	1.522	43.52	46.11	94.383	0.152	0.147	1.037	-0.0193	-0.0503	-0.05033
64	0.2	0.05	0.2	1.25	2.495	43.52	46.11	94.383	0.152	0.147	1.037	-0.0380	-0.0892	-0.08924

Attachment II (cont)

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metric=D50 distance=3 delay=45

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
65	0.1	0.00	0.1	1.11	1.089	49.70	53.11	93.572	0.152	0.138	1.098	-0.0047	0.0035	-0.00473
66	0.1	0.00	0.1	1.25	4.979	49.70	53.11	93.572	0.152	0.138	1.098	-0.0702	-0.0354	-0.07022
67	0.2	0.00	0.2	1.11	0.272	49.70	53.11	93.572	0.152	0.138	1.098	0.0095	0.0035	0.00352
68	0.2	0.00	0.2	1.25	1.245	49.70	53.11	93.572	0.152	0.138	1.098	-0.0074	-0.0354	-0.03538
69	0.1	0.01	0.1	1.11	2.089	49.70	53.11	93.572	0.152	0.138	1.098	-0.0218	-0.0065	-0.02181
70	0.1	0.01	0.1	1.25	5.979	49.70	53.11	93.572	0.152	0.138	1.098	-0.0868	-0.0454	-0.08684
71	0.2	0.01	0.2	1.11	0.522	49.70	53.11	93.572	0.152	0.138	1.098	0.0051	-0.0065	-0.00648
72	0.2	0.01	0.2	1.25	1.495	49.70	53.11	93.572	0.152	0.138	1.098	-0.0117	-0.0454	-0.04538
73	0.1	0.03	0.1	1.11	4.089	49.70	53.11	93.572	0.152	0.138	1.098	-0.0554	-0.0265	-0.05539
74	0.1	0.03	0.1	1.25	7.979	49.70	53.11	93.572	0.152	0.138	1.098	-0.1200	-0.0654	-0.12000
75	0.2	0.03	0.2	1.11	1.022	49.70	53.11	93.572	0.152	0.138	1.098	-0.0036	-0.0265	-0.02648
76	0.2	0.03	0.2	1.25	1.995	49.70	53.11	93.572	0.152	0.138	1.098	-0.0202	-0.0654	-0.06538
77	0.1	0.05	0.1	1.11	6.089	49.70	53.11	93.572	0.152	0.138	1.098	-0.0887	-0.0465	-0.08867
78	0.1	0.05	0.1	1.25	9.979	49.70	53.11	93.572	0.152	0.138	1.098	-0.1531	-0.0854	-0.15310
79	0.2	0.05	0.2	1.11	1.522	49.70	53.11	93.572	0.152	0.138	1.098	-0.0122	-0.0465	-0.04648
80	0.2	0.05	0.2	1.25	2.495	49.70	53.11	93.572	0.152	0.138	1.098	-0.0287	-0.0854	-0.08538

metric=D50 distance=3 delay=75

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
81	0.1	0.00	0.1	1.11	1.089	58.05	58.97	98.432	0.254	0.182	1.394	0.0098	0.0325	0.00979
82	0.1	0.00	0.1	1.25	4.979	58.05	58.97	98.432	0.254	0.182	1.394	-0.1049	-0.0064	-0.10487
83	0.2	0.00	0.2	1.11	0.272	58.05	58.97	98.432	0.254	0.182	1.394	0.0349	0.0325	0.03250
84	0.2	0.00	0.2	1.25	1.245	58.05	58.97	98.432	0.254	0.182	1.394	0.0051	-0.0064	-0.00641
85	0.1	0.01	0.1	1.11	2.089	58.05	58.97	98.432	0.254	0.182	1.394	-0.0202	0.0225	-0.02018
86	0.1	0.01	0.1	1.25	5.979	58.05	58.97	98.432	0.254	0.182	1.394	-0.1339	-0.0164	-0.13388
87	0.2	0.01	0.2	1.11	0.522	58.05	58.97	98.432	0.254	0.182	1.394	0.0271	0.0225	0.02250

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Attachment II (cont)

metric=D50 distance=3 delay=75 (continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
88	0.2	0.01	0.2	1.25	1.495	58.05	58.97	98.432	0.254	0.182	1.394	-0.0024	-0.0164	-0.01641
89	0.1	0.03	0.1	1.11	4.089	58.05	58.97	98.432	0.254	0.182	1.394	-0.0790	0.0025	-0.07895
90	0.1	0.03	0.1	1.25	7.979	58.05	58.97	98.432	0.254	0.182	1.394	-0.1917	-0.0364	-0.19173
91	0.2	0.03	0.2	1.11	1.022	58.05	58.97	98.432	0.254	0.182	1.394	0.0118	0.0025	0.00250
92	0.2	0.03	0.2	1.25	1.995	58.05	58.97	98.432	0.254	0.182	1.394	-0.0174	-0.0364	-0.03641
93	0.1	0.05	0.1	1.11	6.089	58.05	58.97	98.432	0.254	0.182	1.394	-0.1371	-0.0175	-0.13706
94	0.1	0.05	0.1	1.25	9.979	58.05	58.97	98.432	0.254	0.182	1.394	-0.2494	-0.0564	-0.24944
95	0.2	0.05	0.2	1.11	1.522	58.05	58.97	98.432	0.254	0.182	1.394	-0.0033	-0.0175	-0.01750
96	0.2	0.05	0.2	1.25	2.495	58.05	58.97	98.432	0.254	0.182	1.394	-0.0322	-0.0564	-0.05641

metric=D50 distance=5 delay=15

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
97	0.1	0.00	0.1	1.11	1.089	41.05	43.23	94.950	0.116	0.117	0.992	-0.0074	-0.0047	-0.007380
98	0.1	0.00	0.1	1.25	4.979	41.05	43.23	94.950	0.116	0.117	0.992	-0.0540	-0.0436	-0.054013
99	0.2	0.00	0.2	1.11	0.272	41.05	43.23	94.950	0.116	0.117	0.992	0.0027	-0.0047	-0.004716
100	0.2	0.00	0.2	1.25	1.245	41.05	43.23	94.950	0.116	0.117	0.992	-0.0093	-0.0436	-0.043618
101	0.1	0.01	0.1	1.11	2.089	41.05	43.23	94.950	0.116	0.117	0.992	-0.0195	-0.0147	-0.019509
102	0.1	0.01	0.1	1.25	5.979	41.05	43.23	94.950	0.116	0.117	0.992	-0.0659	-0.0536	-0.065879
103	0.2	0.01	0.2	1.11	0.522	41.05	43.23	94.950	0.116	0.117	0.992	-0.0004	-0.0147	-0.014716
104	0.2	0.01	0.2	1.25	1.495	41.05	43.23	94.950	0.116	0.117	0.992	-0.0123	-0.0536	-0.053618
105	0.1	0.03	0.1	1.11	4.089	41.05	43.23	94.950	0.116	0.117	0.992	-0.0434	-0.0347	-0.043429
106	0.1	0.03	0.1	1.25	7.979	41.05	43.23	94.950	0.116	0.117	0.992	-0.0896	-0.0736	-0.089570
107	0.2	0.03	0.2	1.11	1.022	41.05	43.23	94.950	0.116	0.117	0.992	-0.0066	-0.0347	-0.034716
108	0.2	0.03	0.2	1.25	1.995	41.05	43.23	94.950	0.116	0.117	0.992	-0.0184	-0.0736	-0.073618
109	0.1	0.05	0.1	1.11	6.089	41.05	43.23	94.950	0.116	0.117	0.992	-0.0672	-0.0547	-0.067181

Attachment II (cont)

metric=D50 distance=5 delay=15 (continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
110	0.1	0.05	0.1	1.25	9.979	41.05	43.23	94.950	0.116	0.117	0.992	-0.1132	-0.0936	-0.11323
111	0.2	0.05	0.2	1.11	1.522	41.05	43.23	94.950	0.116	0.117	0.992	-0.0127	-0.0547	-0.05472
112	0.2	0.05	0.2	1.25	2.495	41.05	43.23	94.950	0.116	0.117	0.992	-0.0244	-0.0936	-0.09362

metric=D50 distance=5 delay=45

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
113	0.1	0.00	0.1	1.11	1.089	47.26	50.92	92.799	0.123	0.116	1.060	-0.0014	0.0012	-0.00136
114	0.1	0.00	0.1	1.25	4.979	47.26	50.92	92.799	0.123	0.116	1.060	-0.0471	-0.0377	-0.04705
115	0.2	0.00	0.2	1.11	0.272	47.26	50.92	92.799	0.123	0.116	1.060	0.0086	0.0012	0.00117
116	0.2	0.00	0.2	1.25	1.245	47.26	50.92	92.799	0.123	0.116	1.060	-0.0032	-0.0377	-0.03773
117	0.1	0.01	0.1	1.11	2.089	47.26	50.92	92.799	0.123	0.116	1.060	-0.0133	-0.0088	-0.01330
118	0.1	0.01	0.1	1.25	5.979	47.26	50.92	92.799	0.123	0.116	1.060	-0.0586	-0.0477	-0.05862
119	0.2	0.01	0.2	1.11	0.522	47.26	50.92	92.799	0.123	0.116	1.060	0.0056	-0.0088	-0.00883
120	0.2	0.01	0.2	1.25	1.495	47.26	50.92	92.799	0.123	0.116	1.060	-0.0062	-0.0477	-0.04773
121	0.1	0.03	0.1	1.11	4.089	47.26	50.92	92.799	0.123	0.116	1.060	-0.0367	-0.0288	-0.03672
122	0.1	0.03	0.1	1.25	7.979	47.26	50.92	92.799	0.123	0.116	1.060	-0.0817	-0.0677	-0.08170
123	0.2	0.03	0.2	1.11	1.022	47.26	50.92	92.799	0.123	0.116	1.060	-0.0006	-0.0288	-0.02883
124	0.2	0.03	0.2	1.25	1.995	47.26	50.92	92.799	0.123	0.116	1.060	-0.0122	-0.0677	-0.06773
125	0.1	0.05	0.1	1.11	6.089	47.26	50.92	92.799	0.123	0.116	1.060	-0.0599	-0.0488	-0.05989
126	0.1	0.05	0.1	1.25	9.979	47.26	50.92	92.799	0.123	0.116	1.060	-0.1047	-0.0877	-0.10472
127	0.2	0.05	0.2	1.11	1.522	47.26	50.92	92.799	0.123	0.116	1.060	-0.0066	-0.0488	-0.04883
128	0.2	0.05	0.2	1.25	2.495	47.26	50.92	92.799	0.123	0.116	1.060	-0.0181	-0.0877	-0.08773

Attachment II (cont)

metric=D50 distance=5 delay=75

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
129	0.1	0.00	0.1	1.11	1.089	53.60	56.61	94.680	0.279	0.198	1.414	0.0166	0.0456	0.01665
130	0.1	0.00	0.1	1.25	4.979	53.60	56.61	94.680	0.279	0.198	1.414	-0.1196	0.0067	-0.11961
131	0.2	0.00	0.2	1.11	0.272	53.60	56.61	94.680	0.279	0.198	1.414	0.0464	0.0456	0.04564
132	0.2	0.00	0.2	1.25	1.245	53.60	56.61	94.680	0.279	0.198	1.414	0.0110	0.0067	0.00674
133	0.1	0.01	0.1	1.11	2.089	53.60	56.61	94.680	0.279	0.198	1.414	-0.0190	0.0356	-0.01898
134	0.1	0.01	0.1	1.25	5.979	53.60	56.61	94.680	0.279	0.198	1.414	-0.1541	-0.0033	-0.15407
135	0.2	0.01	0.2	1.11	0.522	53.60	56.61	94.680	0.279	0.198	1.414	0.0372	0.0356	0.03564
136	0.2	0.01	0.2	1.25	1.495	53.60	56.61	94.680	0.279	0.198	1.414	0.0021	-0.0033	-0.00326
137	0.1	0.03	0.1	1.11	4.089	53.60	56.61	94.680	0.279	0.198	1.414	-0.0888	0.0156	-0.08884
138	0.1	0.03	0.1	1.25	7.979	53.60	56.61	94.680	0.279	0.198	1.414	-0.2227	-0.0233	-0.22273
139	0.2	0.03	0.2	1.11	1.022	53.60	56.61	94.680	0.279	0.198	1.414	0.0191	0.0156	0.01564
140	0.2	0.03	0.2	1.25	1.995	53.60	56.61	94.680	0.279	0.198	1.414	-0.0157	-0.0233	-0.02326
141	0.1	0.05	0.1	1.11	6.089	53.60	56.61	94.680	0.279	0.198	1.414	-0.1578	-0.0044	-0.15784
142	0.1	0.05	0.1	1.25	9.979	53.60	56.61	94.680	0.279	0.198	1.414	-0.2912	-0.0433	-0.29120
143	0.2	0.05	0.2	1.11	1.522	53.60	56.61	94.680	0.279	0.198	1.414	0.0011	-0.0044	-0.00436
144	0.2	0.05	0.2	1.25	2.495	53.60	56.61	94.680	0.279	0.198	1.414	-0.0333	-0.0433	-0.04326

metric=Span distance=1 delay=15

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
145	0.1	0.00	0.1	1.11	1.089	1.627	1.827	89.055	0.053	0.273	0.196	-0.1188	-0.0576	-0.11882
146	0.1	0.00	0.1	1.25	4.979	1.627	1.827	89.055	0.053	0.273	0.196	-0.3732	-0.0965	-0.37324
147	0.2	0.00	0.2	1.11	0.272	1.627	1.827	89.055	0.053	0.273	0.196	-0.0649	-0.0576	-0.06491
148	0.2	0.00	0.2	1.25	1.245	1.627	1.827	89.055	0.053	0.273	0.196	-0.1291	-0.0965	-0.12905
149	0.1	0.01	0.1	1.11	2.089	1.627	1.827	89.055	0.053	0.273	0.196	-0.1844	-0.0676	-0.18439
150	0.1	0.01	0.1	1.25	5.979	1.627	1.827	89.055	0.053	0.273	0.196	-0.4385	-0.1065	-0.43851
151	0.2	0.01	0.2	1.11	0.522	1.627	1.827	89.055	0.053	0.273	0.196	-0.0815	-0.0676	-0.08147

Attachment II (cont)

metric=Span distance=1 delay=15 (continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
152	0.2	0.01	0.2	1.25	1.495	1.627	1.827	89.055	0.053	0.273	0.196	-0.1455	-0.1065	-0.14546
153	0.1	0.03	0.1	1.11	4.089	1.627	1.827	89.055	0.053	0.273	0.196	-0.3151	-0.0876	-0.31512
154	0.1	0.03	0.1	1.25	7.979	1.627	1.827	89.055	0.053	0.273	0.196	-0.5690	-0.1265	-0.56902
155	0.2	0.03	0.2	1.11	1.022	1.627	1.827	89.055	0.053	0.273	0.196	-0.1144	-0.0876	-0.11443
156	0.2	0.03	0.2	1.25	1.995	1.627	1.827	89.055	0.053	0.273	0.196	-0.1782	-0.1265	-0.17822
157	0.1	0.05	0.1	1.11	6.089	1.627	1.827	89.055	0.053	0.273	0.196	-0.4457	-0.1076	-0.44568
158	0.1	0.05	0.1	1.25	9.979	1.627	1.827	89.055	0.053	0.273	0.196	-0.6995	-0.1465	-0.69950
159	0.2	0.05	0.2	1.11	1.522	1.627	1.827	89.055	0.053	0.273	0.196	-0.1473	-0.1076	-0.14726
160	0.2	0.05	0.2	1.25	2.495	1.627	1.827	89.055	0.053	0.273	0.196	-0.2109	-0.1465	-0.21094

metric=Span distance=1 delay=45

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
161	0.1	0.00	0.1	1.11	1.089	1.540	1.674	91.991	0.054	0.157	0.341	-0.0338	-0.0209	-0.03379
162	0.1	0.00	0.1	1.25	4.979	1.540	1.674	91.991	0.054	0.157	0.341	-0.1169	-0.0598	-0.11687
163	0.2	0.00	0.2	1.11	0.272	1.540	1.674	91.991	0.054	0.157	0.341	-0.0161	-0.0209	-0.02094
164	0.2	0.00	0.2	1.25	1.245	1.540	1.674	91.991	0.054	0.157	0.341	-0.0371	-0.0598	-0.05984
165	0.1	0.01	0.1	1.11	2.089	1.540	1.674	91.991	0.054	0.157	0.341	-0.0552	-0.0309	-0.05525
166	0.1	0.01	0.1	1.25	5.979	1.540	1.674	91.991	0.054	0.157	0.341	-0.1381	-0.0698	-0.13815
167	0.2	0.01	0.2	1.11	0.522	1.540	1.674	91.991	0.054	0.157	0.341	-0.0215	-0.0309	-0.03094
168	0.2	0.01	0.2	1.25	1.495	1.540	1.674	91.991	0.054	0.157	0.341	-0.0425	-0.0698	-0.06984
169	0.1	0.03	0.1	1.11	4.089	1.540	1.674	91.991	0.054	0.157	0.341	-0.0979	-0.0509	-0.09792
170	0.1	0.03	0.1	1.25	7.979	1.540	1.674	91.991	0.054	0.157	0.341	-0.1807	-0.0898	-0.18067
171	0.2	0.03	0.2	1.11	1.022	1.540	1.674	91.991	0.054	0.157	0.341	-0.0323	-0.0509	-0.05094
172	0.2	0.03	0.2	1.25	1.995	1.540	1.674	91.991	0.054	0.157	0.341	-0.0532	-0.0898	-0.08984
173	0.1	0.05	0.1	1.11	6.089	1.540	1.674	91.991	0.054	0.157	0.341	-0.1405	-0.0709	-0.14048

Attachment II (cont)

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metric=Span distance=1 delay=45 (continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
174	0.1	0.05	0.1	1.25	9.979	1.540	1.674	91.991	0.054	0.157	0.341	-0.2232	-0.1098	-0.22318
175	0.2	0.05	0.2	1.11	1.522	1.540	1.674	91.991	0.054	0.157	0.341	-0.0431	-0.0709	-0.07094
176	0.2	0.05	0.2	1.25	2.495	1.540	1.674	91.991	0.054	0.157	0.341	-0.0639	-0.1098	-0.10984

metric=Span distance=1 delay=75

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
177	0.1	0.00	0.1	1.11	1.089	1.535	1.694	90.653	0.071	0.221	0.319	-0.0711	-0.0360	-0.07114
178	0.1	0.00	0.1	1.25	4.979	1.535	1.694	90.653	0.071	0.221	0.319	-0.2332	-0.0749	-0.23319
179	0.2	0.00	0.2	1.11	0.272	1.535	1.694	90.653	0.071	0.221	0.319	-0.0367	-0.0360	-0.03671
180	0.2	0.00	0.2	1.25	1.245	1.535	1.694	90.653	0.071	0.221	0.319	-0.0777	-0.0749	-0.07767
181	0.1	0.01	0.1	1.11	2.089	1.535	1.694	90.653	0.071	0.221	0.319	-0.1129	-0.0460	-0.11294
182	0.1	0.01	0.1	1.25	5.979	1.535	1.694	90.653	0.071	0.221	0.319	-0.2747	-0.0849	-0.27473
183	0.2	0.01	0.2	1.11	0.522	1.535	1.694	90.653	0.071	0.221	0.319	-0.0473	-0.0460	-0.04730
184	0.2	0.01	0.2	1.25	1.495	1.535	1.694	90.653	0.071	0.221	0.319	-0.0881	-0.0849	-0.08813
185	0.1	0.03	0.1	1.11	4.089	1.535	1.694	90.653	0.071	0.221	0.319	-0.1962	-0.0660	-0.19618
186	0.1	0.03	0.1	1.25	7.979	1.535	1.694	90.653	0.071	0.221	0.319	-0.3578	-0.1049	-0.35779
187	0.2	0.03	0.2	1.11	1.022	1.535	1.694	90.653	0.071	0.221	0.319	-0.0683	-0.0660	-0.06834
188	0.2	0.03	0.2	1.25	1.995	1.535	1.694	90.653	0.071	0.221	0.319	-0.1090	-0.1049	-0.10900
189	0.1	0.05	0.1	1.11	6.089	1.535	1.694	90.653	0.071	0.221	0.319	-0.2793	-0.0860	-0.27929
190	0.1	0.05	0.1	1.25	9.979	1.535	1.694	90.653	0.071	0.221	0.319	-0.4408	-0.1249	-0.44083
191	0.2	0.05	0.2	1.11	1.522	1.535	1.694	90.653	0.071	0.221	0.319	-0.0893	-0.0860	-0.08927
192	0.2	0.05	0.2	1.25	2.495	1.535	1.694	90.653	0.071	0.221	0.319	-0.1298	-0.1249	-0.12985

Attachment II (cont)

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metric=Span distance=3 delay=15

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
193	0.1	0.00	0.1	1.11	1.089	1.644	1.680	97.859	0.067	0.146	0.455	-0.0319	-0.0235	-0.03188
194	0.1	0.00	0.1	1.25	4.979	1.644	1.680	97.859	0.067	0.146	0.455	-0.1006	-0.0624	-0.10055
195	0.2	0.00	0.2	1.11	0.272	1.644	1.680	97.859	0.067	0.146	0.455	-0.0174	-0.0235	-0.02348
196	0.2	0.00	0.2	1.25	1.245	1.644	1.680	97.859	0.067	0.146	0.455	-0.0346	-0.0624	-0.06238
197	0.1	0.01	0.1	1.11	2.089	1.644	1.680	97.859	0.067	0.146	0.455	-0.0495	-0.0335	-0.04954
198	0.1	0.01	0.1	1.25	5.979	1.644	1.680	97.859	0.067	0.146	0.455	-0.1182	-0.0724	-0.11819
199	0.2	0.01	0.2	1.11	0.522	1.644	1.680	97.859	0.067	0.146	0.455	-0.0219	-0.0335	-0.03348
200	0.2	0.01	0.2	1.25	1.495	1.644	1.680	97.859	0.067	0.146	0.455	-0.0390	-0.0724	-0.07238
201	0.1	0.03	0.1	1.11	4.089	1.644	1.680	97.859	0.067	0.146	0.455	-0.0848	-0.0535	-0.08484
202	0.1	0.03	0.1	1.25	7.979	1.644	1.680	97.859	0.067	0.146	0.455	-0.1535	-0.0924	-0.15348
203	0.2	0.03	0.2	1.11	1.022	1.644	1.680	97.859	0.067	0.146	0.455	-0.0307	-0.0535	-0.05348
204	0.2	0.03	0.2	1.25	1.995	1.644	1.680	97.859	0.067	0.146	0.455	-0.0479	-0.0924	-0.09238
205	0.1	0.05	0.1	1.11	6.089	1.644	1.680	97.859	0.067	0.146	0.455	-0.1201	-0.0735	-0.12013
206	0.1	0.05	0.1	1.25	9.979	1.644	1.680	97.859	0.067	0.146	0.455	-0.1888	-0.1124	-0.18877
207	0.2	0.05	0.2	1.11	1.522	1.644	1.680	97.859	0.067	0.146	0.455	-0.0395	-0.0735	-0.07348
208	0.2	0.05	0.2	1.25	2.495	1.644	1.680	97.859	0.067	0.146	0.455	-0.0567	-0.1124	-0.11238

metric=Span distance=3 delay=45

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
209	0.1	0.00	0.1	1.11	1.089	1.572	1.581	99.417	0.063	0.121	0.520	-0.0218	-0.0191	-0.021782
210	0.1	0.00	0.1	1.25	4.979	1.572	1.581	99.417	0.063	0.121	0.520	-0.0700	-0.0580	-0.069975
211	0.2	0.00	0.2	1.11	0.272	1.572	1.581	99.417	0.063	0.121	0.520	-0.0116	-0.0191	-0.019114
212	0.2	0.00	0.2	1.25	1.245	1.572	1.581	99.417	0.063	0.121	0.520	-0.0237	-0.0580	-0.058016
213	0.1	0.01	0.1	1.11	2.089	1.572	1.581	99.417	0.063	0.121	0.520	-0.0342	-0.0291	-0.034182
214	0.1	0.01	0.1	1.25	5.979	1.572	1.581	99.417	0.063	0.121	0.520	-0.0824	-0.0680	-0.082355
215	0.2	0.01	0.2	1.11	0.522	1.572	1.581	99.417	0.063	0.121	0.520	-0.0147	-0.0291	-0.029114

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Attachment II (cont)

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metric=Span distance=3 delay=45 (continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
216	0.2	0.01	0.2	1.25	1.495	1.572	1.581	99.417	0.063	0.121	0.520	-0.0268	-0.0680	-0.06802
217	0.1	0.03	0.1	1.11	4.089	1.572	1.581	99.417	0.063	0.121	0.520	-0.0590	-0.0491	-0.05895
218	0.1	0.03	0.1	1.25	7.979	1.572	1.581	99.417	0.063	0.121	0.520	-0.1071	-0.0880	-0.10711
219	0.2	0.03	0.2	1.11	1.022	1.572	1.581	99.417	0.063	0.121	0.520	-0.0210	-0.0491	-0.04911
220	0.2	0.03	0.2	1.25	1.995	1.572	1.581	99.417	0.063	0.121	0.520	-0.0330	-0.0880	-0.08802
221	0.1	0.05	0.1	1.11	6.089	1.572	1.581	99.417	0.063	0.121	0.520	-0.0837	-0.0691	-0.08371
222	0.1	0.05	0.1	1.25	9.979	1.572	1.581	99.417	0.063	0.121	0.520	-0.1319	-0.1080	-0.13186
223	0.2	0.05	0.2	1.11	1.522	1.572	1.581	99.417	0.063	0.121	0.520	-0.0272	-0.0691	-0.06911
224	0.2	0.05	0.2	1.25	2.495	1.572	1.581	99.417	0.063	0.121	0.520	-0.0392	-0.1080	-0.10802

metric=Span distance=3 delay=75

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
225	0.1	0.00	0.1	1.11	1.089	1.567	1.547	101.351	0.076	0.088	0.865	-0.0079	-0.0111	-0.011132
226	0.1	0.00	0.1	1.25	4.979	1.567	1.547	101.351	0.076	0.088	0.865	-0.0345	-0.0500	-0.050034
227	0.2	0.00	0.2	1.11	0.272	1.567	1.547	101.351	0.076	0.088	0.865	-0.0022	-0.0111	-0.011132
228	0.2	0.00	0.2	1.25	1.245	1.567	1.547	101.351	0.076	0.088	0.865	-0.0090	-0.0500	-0.050034
229	0.1	0.01	0.1	1.11	2.089	1.567	1.547	101.351	0.076	0.088	0.865	-0.0148	-0.0211	-0.021132
230	0.1	0.01	0.1	1.25	5.979	1.567	1.547	101.351	0.076	0.088	0.865	-0.0413	-0.0600	-0.060034
231	0.2	0.01	0.2	1.11	0.522	1.567	1.547	101.351	0.076	0.088	0.865	-0.0039	-0.0211	-0.021132
232	0.2	0.01	0.2	1.25	1.495	1.567	1.547	101.351	0.076	0.088	0.865	-0.0107	-0.0600	-0.060034
233	0.1	0.03	0.1	1.11	4.089	1.567	1.547	101.351	0.076	0.088	0.865	-0.0285	-0.0411	-0.041132
234	0.1	0.03	0.1	1.25	7.979	1.567	1.547	101.351	0.076	0.088	0.865	-0.0549	-0.0800	-0.080034
235	0.2	0.03	0.2	1.11	1.022	1.567	1.547	101.351	0.076	0.088	0.865	-0.0074	-0.0411	-0.041132
236	0.2	0.03	0.2	1.25	1.995	1.567	1.547	101.351	0.076	0.088	0.865	-0.0141	-0.0800	-0.080034
237	0.1	0.05	0.1	1.11	6.089	1.567	1.547	101.351	0.076	0.088	0.865	-0.0421	-0.0611	-0.061132

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Attachment II (cont)

metric=Span distance=3 delay=75 (continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
238	0.1	0.05	0.1	1.25	9.979	1.567	1.547	101.351	0.076	0.088	0.865	-0.0686	-0.1000	-0.10003
239	0.2	0.05	0.2	1.11	1.522	1.567	1.547	101.351	0.076	0.088	0.865	-0.0109	-0.0611	-0.06113
240	0.2	0.05	0.2	1.25	2.495	1.567	1.547	101.351	0.076	0.088	0.865	-0.0176	-0.1000	-0.10003

metric=Span distance=5 delay=15

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
241	0.1	0.00	0.1	1.11	1.089	1.484	1.477	100.460	0.098	0.160	0.611	-0.0359	-0.0228	-0.03593
242	0.1	0.00	0.1	1.25	4.979	1.484	1.477	100.460	0.098	0.160	0.611	-0.1212	-0.0617	-0.12118
243	0.2	0.00	0.2	1.11	0.272	1.484	1.477	100.460	0.098	0.160	0.611	-0.0179	-0.0228	-0.02277
244	0.2	0.00	0.2	1.25	1.245	1.484	1.477	100.460	0.098	0.160	0.611	-0.0394	-0.0617	-0.06168
245	0.1	0.01	0.1	1.11	2.089	1.484	1.477	100.460	0.098	0.160	0.611	-0.0579	-0.0328	-0.05788
246	0.1	0.01	0.1	1.25	5.979	1.484	1.477	100.460	0.098	0.160	0.611	-0.1431	-0.0717	-0.14307
247	0.2	0.01	0.2	1.11	0.522	1.484	1.477	100.460	0.098	0.160	0.611	-0.0235	-0.0328	-0.03277
248	0.2	0.01	0.2	1.25	1.495	1.484	1.477	100.460	0.098	0.160	0.611	-0.0448	-0.0717	-0.07168
249	0.1	0.03	0.1	1.11	4.089	1.484	1.477	100.460	0.098	0.160	0.611	-0.1017	-0.0528	-0.10169
250	0.1	0.03	0.1	1.25	7.979	1.484	1.477	100.460	0.098	0.160	0.611	-0.1868	-0.0917	-0.18684
251	0.2	0.03	0.2	1.11	1.022	1.484	1.477	100.460	0.098	0.160	0.611	-0.0345	-0.0528	-0.05277
252	0.2	0.03	0.2	1.25	1.995	1.484	1.477	100.460	0.098	0.160	0.611	-0.0558	-0.0917	-0.09168
253	0.1	0.05	0.1	1.11	6.089	1.484	1.477	100.460	0.098	0.160	0.611	-0.1455	-0.0728	-0.14548
254	0.1	0.05	0.1	1.25	9.979	1.484	1.477	100.460	0.098	0.160	0.611	-0.2306	-0.1117	-0.23061
255	0.2	0.05	0.2	1.11	1.522	1.484	1.477	100.460	0.098	0.160	0.611	-0.0454	-0.0728	-0.07277
256	0.2	0.05	0.2	1.25	2.495	1.484	1.477	100.460	0.098	0.160	0.611	-0.0668	-0.1117	-0.11168

Attachment II (cont)

metric=Span distance=5 delay=45

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
257	0.1	0.00	0.1	1.11	1.089	1.391	1.384	100.494	0.094	0.158	0.597	-0.0357	-0.0230	-0.03574
258	0.1	0.00	0.1	1.25	4.979	1.391	1.384	100.494	0.094	0.158	0.597	-0.1194	-0.0619	-0.11943
259	0.2	0.00	0.2	1.11	0.272	1.391	1.384	100.494	0.094	0.158	0.597	-0.0181	-0.0230	-0.02304
260	0.2	0.00	0.2	1.25	1.245	1.391	1.384	100.494	0.094	0.158	0.597	-0.0391	-0.0619	-0.06195
261	0.1	0.01	0.1	1.11	2.089	1.391	1.384	100.494	0.094	0.158	0.597	-0.0573	-0.0330	-0.05729
262	0.1	0.01	0.1	1.25	5.979	1.391	1.384	100.494	0.094	0.158	0.597	-0.1409	-0.0719	-0.14092
263	0.2	0.01	0.2	1.11	0.522	1.391	1.384	100.494	0.094	0.158	0.597	-0.0235	-0.0330	-0.03304
264	0.2	0.01	0.2	1.25	1.495	1.391	1.384	100.494	0.094	0.158	0.597	-0.0445	-0.0719	-0.07195
265	0.1	0.03	0.1	1.11	4.089	1.391	1.384	100.494	0.094	0.158	0.597	-0.1003	-0.0530	-0.10030
266	0.1	0.03	0.1	1.25	7.979	1.391	1.384	100.494	0.094	0.158	0.597	-0.1839	-0.0919	-0.18390
267	0.2	0.03	0.2	1.11	1.022	1.391	1.384	100.494	0.094	0.158	0.597	-0.0343	-0.0530	-0.05304
268	0.2	0.03	0.2	1.25	1.995	1.391	1.384	100.494	0.094	0.158	0.597	-0.0553	-0.0919	-0.09195
269	0.1	0.05	0.1	1.11	6.089	1.391	1.384	100.494	0.094	0.158	0.597	-0.1433	-0.0730	-0.14328
270	0.1	0.05	0.1	1.25	9.979	1.391	1.384	100.494	0.094	0.158	0.597	-0.2269	-0.1119	-0.22686
271	0.2	0.05	0.2	1.11	1.522	1.391	1.384	100.494	0.094	0.158	0.597	-0.0451	-0.0730	-0.07304
272	0.2	0.05	0.2	1.25	2.495	1.391	1.384	100.494	0.094	0.158	0.597	-0.0660	-0.1119	-0.11195

metric=Span distance=5 delay=75

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
273	0.1	0.00	0.1	1.11	1.089	1.436	1.427	100.594	0.127	0.177	0.717	-0.0384	-0.0202	-0.03845
274	0.1	0.00	0.1	1.25	4.979	1.436	1.427	100.594	0.127	0.177	0.717	-0.1413	-0.0591	-0.14126
275	0.2	0.00	0.2	1.11	0.272	1.436	1.427	100.594	0.127	0.177	0.717	-0.0166	-0.0202	-0.02019
276	0.2	0.00	0.2	1.25	1.245	1.436	1.427	100.594	0.127	0.177	0.717	-0.0426	-0.0591	-0.05909
277	0.1	0.01	0.1	1.11	2.089	1.436	1.427	100.594	0.127	0.177	0.717	-0.0649	-0.0302	-0.06495
278	0.1	0.01	0.1	1.25	5.979	1.436	1.427	100.594	0.127	0.177	0.717	-0.1676	-0.0691	-0.16764
279	0.2	0.01	0.2	1.11	0.522	1.436	1.427	100.594	0.127	0.177	0.717	-0.0233	-0.0302	-0.03019

Attachment II (cont)

metric=Span distance=5 delay=75
(continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
280	0.2	0.01	0.2	1.25	1.495	1.436	1.427	100.594	0.127	0.177	0.717	-0.0492	-0.0691	-0.06909
281	0.1	0.03	0.1	1.11	4.089	1.436	1.427	100.594	0.127	0.177	0.717	-0.1178	-0.0502	-0.11778
282	0.1	0.03	0.1	1.25	7.979	1.436	1.427	100.594	0.127	0.177	0.717	-0.2204	-0.0891	-0.22037
283	0.2	0.03	0.2	1.11	1.022	1.436	1.427	100.594	0.127	0.177	0.717	-0.0367	-0.0502	-0.05019
284	0.2	0.03	0.2	1.25	1.995	1.436	1.427	100.594	0.127	0.177	0.717	-0.0625	-0.0891	-0.08909
285	0.1	0.05	0.1	1.11	6.089	1.436	1.427	100.594	0.127	0.177	0.717	-0.1705	-0.0702	-0.17053
286	0.1	0.05	0.1	1.25	9.979	1.436	1.427	100.594	0.127	0.177	0.717	-0.2731	-0.1091	-0.27309
287	0.2	0.05	0.2	1.11	1.522	1.436	1.427	100.594	0.127	0.177	0.717	-0.0499	-0.0702	-0.07019
288	0.2	0.05	0.2	1.25	2.495	1.436	1.427	100.594	0.127	0.177	0.717	-0.0757	-0.1091	-0.10909

BIOEQUIVALENCY COMMENTS

ANDA: 75-824 APPLICANT: Roxane Laboratories

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,

/S/

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

CC: ANDA 75-824
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney
HFD-652/ Y. Huang
HFD-655/ GJP Sing'
HFD-617/ K. Scardina
HFD-650/ D. Connc

/S/ 5/15/2001
/S/ 5/16/01
/S/ 5/18/2001
5/16/01
5/22/2001

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BIOEQUIVALENCY - ACCEPTABLE

Submission Date: December 18, 2000

STUDY AMENDMENT (STA)

Strengths:
Outcome: AC

NOTE:
AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:

The *in vitro* performance testing conducted on Roxane Laboratories' Butorphanol Tartrate Nasal Spray Pump, 10 mg/mL comparing it with the reference product, Stadol®, nasal solution (Bristol-Myers) has been found acceptable.

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-824 SPONSOR : Roxane Laboratories
DRUG AND DOSAGE FORM: Butorphanol Tartrate Nasal Spray,
STRENGTH(S): 10 mg/mL
TYPES OF STUDIES: *In vitro*

TESTING LABORATORY: _____

STUDY SUMMARY: Acceptable

DISSOLUTION: NA

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status:	Inspection results: Acceptable
First Generic YES New facility NO For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date) Aug 01, 2001	

PRIMARY REVIEWER: James Chaney BRANCH: I

INITIAL /S/ DATE: 5/21/2001

TEAM LEADER: Yih-Chain Huang BRANCH: I

INITIAL: /S/ DATE: 5/21/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

for INITIAL : /S/ _____ DATE : 11/15/2001

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-824 SPONSOR : Roxane Laboratories
DRUG AND DOSAGE FORM: Butorphanol Tartrate Nasal Spray,
STRENGTH(S): 10 mg/mL
TYPES OF STUDIES: *In vitro*

TESTING LABORATORY: ~~~~~~~~~~

STUDY SUMMARY: Based on an acceptable response from Roxane to the Form 483 from the DSI inspection the study remains acceptable.

DISSOLUTION: NA

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status:	Inspection results: Acceptable
First Generic YES New facility NO For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date) 7/27/01	

PRIMARY REVIEWER: James Chaney BRANCH: I

INITIAL: _ /S/ _____ DATE: 10/26/2001

TEAM LEADER: Yih-Chain Huang BRANCH: I

INITIAL: /S/ DATE: 10/26/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

INITIAL . /S/ DATE : 11/13/01

CC: ANDA 75-824
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney /S/ 10/26/2001
HFD-652/ Y. Huang /S/ 10/26/2001
HFD-617/ K. Scardina
HFD-650/ D. Conner /S/ 11/13/01
HFD-48 S. Subraman

V:\FIRMSNZ\ROXANE\LTRS&REV\75824ins.801

BIOEQUIVALENCY - ACCEPTABLE

1. OTHERS (OTH) - US Document Dated August 2, 2001 (1)
   Strength: 10 mg/mL
   (Audit Report Submitted August 1, 2001)
   Outcome: AC

2. STUDY AMENDMENT (STA)
   Strength: 10 mg/mL
   (Amendment in response to DSI report
   Submitted October 8, 2001)
   Outcome: AC

NOTE:

IC - Incomplete
AC - Acceptable
UN - Unacceptable
NC - No Action

Outcome Decision: AC - Acceptable

WINBIO COMMENT: Based on an acceptable response from Roxane to the Form 483 from the DSI inspection the study remains acceptable.

BIOEQUIVALENCY COMMENTS

ANDA: 75-824 APPLICANT: Roxane Laboratories

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,

/S/

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

8/2/01
10/8/01
DST
Rep

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pages of trade secret and/or confidential commercial information

BIOEQUIVALENCY ACCEPTABLE

ANDA: 75-824 APPLICANT: Roxane Laboratories

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 be advised for the future that (1) per 21 CFR 320.63 you should assure the proper retention of samples by the testing laboratories and clinics for all bioavailability or bioequivalence studies and (2) in your bioequivalence studies you should consistently follow parameters established during pre-study method validations.

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,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-824

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: **75-824** Date of Submission: **March 24, 2000**

Applicant's Name: **Roxane laboratories, Inc.**

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

Labeling Deficiencies:

1. GENERAL

   a. Revise the storage temperature statement on the labels and labeling to read "Store at controlled
   room temperature, 15° to 30°C (59° to 86°F) [see USP]" .

   b. Please explain exactly how your proposed " [redacted] " labeling configuration will be used.

2. CONTAINER - 2.5 mL

   a. See general comment above.

   b. It is very difficult to read your proposed label. Please assure that your label appears with sufficient prominence.

   c. Relocate the "Rx only" statement to the principal display panel, if space permits.

   d. Revise to read "Usual Dosage: Read enclosed...".

3. CARTON – 1 x 2.5 mL

   a. See general comment above.

   b. Boxed statement (ATTENTION PHARMACIST:... BEFORE DISPENSING.)

   Relocate this statement from the patient instructions leaflet to appear on the carton labeling and revise to read as follows:

   ATTENTION PHARMACIST: Please remove the... before dispensing

4. PATIENT INSTRUCTIONS

   a. See comment (b) under CARTON.

   b. Please explain whether the patient instructions will be printed on the carton or a separate patient instructions leaflet will be provided for dispensing to patients. Refer to comments (1)(b) and (5) as well.

5. 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. You may submit this patient medication guide with the patient instructions printed together as one labeling piece or separately from the patient instruction sheet. We have included a copy of the

approval letter for this piece as well as a copy of the medication guide. Please note that the text of this medication guide must also appear at the end of the insert labeling (after the pharmacist assembly instructions) and must be referred to in the PRECAUTIONS, Information for Patients subsection. See 21 CFR 201.57(f)(2) for guidance.

6. INSERT

a. GENERAL

i. See general comment above.

ii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

iii. It is preferable to use "to" rather than a "—" when expressing a range of values.

iv. It is preferable to use "mcg" rather than "—"

v. Please be advised that the following comments are based on the last approved innovator's insert labeling (approved in draft on April 16, 1999). We have attached one copy of this insert labeling for your reference.

b. DESCRIPTION

i. First paragraph:

A) Revise the chemical name to be same as the second name appearing in the USP for "butorphanol tartrate".

B) Use a bullet (•) rather a "—" in the molecular formula.

ii. Last paragraph:

A) Third sentence to the last:

... 14 to 15 doses of butorphanol tartrate nasal spray. [add "nasal spray"]

B) Last sentence:

... 8 to 10 doses of butorphanol tartrate nasal spray. [add "nasal spray"]

c. CLINICAL PHARMACOLOGY

i. General Pharmacology and Mechanism of Action

A) Revise the first paragraph to read as follows.

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.

B) Sixth paragraph:

...by 10 to 12 mg doses... [rather than "—"]

ii. Pharmacodynamics – First paragraph:

...within 15 minutes for intramuscular... [rather than "—"]

iii. Pharmacokinetics

A) Third paragraph:

Following its initial absorption/... [add "initial"]

B) Figure 1:

Increase the prominence so that it becomes legible, the legends in particular.

C) The paragraph starting "The major metabolite..."

Revise the second and last sentences to read as follows:

...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).

D) Last paragraph:

For further recommendations refer to Hepatic and Renal Disease, Drug Interactions, and Geriatric use in PRECAUTIONS section and to Individualization of Dosage in CLINICAL PHARMACOLOGY section below.

iv. Clinical Trials

Let the second sentence "Studies with..." start a new second paragraph.

v. Individualization of Dosage

A) Delete the first and third paragraphs.

B) Second paragraph:

... impairment requires extra... [delete "

C) 5th paragraph:

...repeated in 3 to 4 hours as required <u>after the second dose</u> of the sequence".

d. WARNINGS (Drug Abuse and Dependence) - Revise to read as follows:

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... and dependence. (See DRUG ABUSE AND DEPENDENCE section below.)

e. PRECAUTIONS

i. Cardiovascular Effects – First paragraph:

Relocate "(see CLINICAL PHARMACOLOGY" to the end of this paragraph.

ii. Information for Patients

A) Revise this subsection heading to read "Use in Ambulatory Patients".

B) First sentence :

Opioid analgesics, including butorphanol, impair...

C) Second sentence:

...the first hour after dosing. These effects may persist for varying periods of time after dosing. Patients who have taken...

D) Revise the item 3 to read as follows.

Butorphanol is one of a class of drugs known to be abused and thus should be handled accordingly (see DRUG ABUSE AND DEPENDENCE section).

E) Revise the item 4 to read as follows.

Patients should be instructed on the proper use of butorphanol tartrate nasal spray (see Patient Instructions).

iii. Drug Interactions

A) Include the following text as the second and third paragraphs.

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.

The pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol tartrate nasal spray were not affected by the coadministration 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.

B) Second paragraph:

... of drugs (erythromycin, theophylline, etc), but... [delete "

iv.

Delete this subsection in its entirety and replace with the text "**Information for Patients** (see See also comment under (5) above.

v. Carcinogenesis,... 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) Last paragraph:

...(944 mg/m^2) has a reduced... [rather than "

vi. Pregnancy. Pregnancy Category C – First paragraph, second sentence:

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

f. ADVERSE REACTIONS

Revise this section throughout the text to be same as the innovator's.

g. DRUG ABUSE AND DEPENDENCE

i. Revise the first two paragraphs to read 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 frequency 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.

ii. Clinical Trial Experience

Revise this subsection to be same as the innovator's .

iii. Postmarketing Experience

Delete the second paragraph.

h. OVERDOSAGE

i. Clinical Manifestations

Revise the first paragraph to be same as the innovator's

ii. Treatment – Add the following as the last paragraph.

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

i. DOSAGE AND ADMINISTRATION

i. Use for Pain – Second paragraph:

... repeated in 3 to 4 hours as required <u>after the second dose</u> of the sequence.

ii. Delete the "

iii. Safety and handling – Include the following as the last sentence of the last paragraph.

The unit should be disposed of by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

j. HOW SUPPLIED:

i. Revise the first sentence to read as follows:

Butorphanol tartrate nasal spray is supplied in a child-resistant vial containing a 2.5 mL bottle of nasal spray solution (10 mg/mL) and a metered-dose spray pump.....instruction leaflet and medication guide.

ii. Please include the full text of the MEDICATION GUIDE 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.

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.

/S/

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

Attachments: Innovator's package insert labeling and MEDICATION GUIDE

Redacted 3

pages of trade secret and/or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-824

CORRESPONDENCE

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT
N/A
FPL

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

February 7, 2002

Attention: Jeen Min

Re: ANDA 75-824
Butorphanol Tartrate Nasal Spray, 10mg/mL
LABELING AMENDMENT

Dear Mr. Min:

We wish to amend ANDA 75-824. This is in response to the labeling revision requested by Mr. Chen Park on January 28, 2002 as a result of the revision on the PRECAUTIONS section of the package insert for Stadol NS (butorphanol tartrate) Nasal Spray, the reference listed drug. Attached is a copy of the request from Mr. Park. The PRECAUTIONS section of Roxane's package insert was revised to match the Stadol NS package insert revision.

Attached are 12 copies of the final printed labeling and 5 copies of the side-by-side comparison of Roxane's revised package insert with the previous revision submitted in the Fax Amendment dated May 3, 2001.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products, Roxane Laboratories, Inc. She can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 11 2002

Elizabeth A. Ernst, R.N., B.S.N.
Associate Director, Regulatory Affairs, DRA-Multisource Products for Roxane Laboratories, Inc.

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Certification of Submission of District Office Copy

Roxane Laboratories, Inc. hereby certifies that a third (field) copy of the Labeling Amendment to ANDA 75-824 for Butorphanol Tartrate Nasal Spray, 10 mg/mL has been submitted to the Cincinnati, Ohio District Office in accordance with 21 CFR 314.94(d)(5) and that the field copy is a "true copy" of the technical sections contained in the archival and review copies.

Elizabeth Ernst
Associate Director, DRA-Multisource Products

2/7/02
Date

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AM

February 1, 2002

Attention: Jeen Min

Re: ANDA 75-824
Butorphanol Tartrate Nasal Spray, 10mg/mL
MINOR AMENDMENT

Dear Mr. Min:

We wish to amend ANDA 75-824. This is in response to your letter dated December 18, 2001. This is to notify you that the re-inspection of Roxane's facility for the cGMP related issues has been completed. The re-inspection was conducted by FDA investigators Frederick M. Lochner and Phillip M. Pontikos from the Cincinnati FDA District Office on January 14, through 18, January 23 and 24, 2002. At the wrap up meeting on January 24, 2002, the FDA investigators told Roxane Management that they would recommend acceptance of the pending liquid ANDAs (which includes Butorphanol Tartrate Nasal Spray) whose approvals were withheld as a result of the cGMP deficiencies. In addition, the reinspection of Roxane's facility did not require any significant revision of any procedure, control or practices affecting this application.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs at (614) 241-4133.

CENTER FOR DRUG
FEB 04 2002
EVALUATION AND RESEARCH

Respectfully,

Virginia J. Fojas for

Elizabeth Ernst
Associate Director, DRA-Multisource Products

Elizabeth A. Ernst, R.N., B.S.N.
Associate Director, Regulatory Affairs, DRA-Multisource Products for Roxane Laboratories, Inc.

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AA

January 17, 2002

removed from EES 1/24/02 IS

Re: ANDA 75-824
Butorphanol Tartrate Nasal Spray, 10mg/mL
GRATUITOUS AMENDMENT

Dear Mr. Min:

We wish to amend ANDA 75-824. Enclosed please find a revision of Section X of the ANDA – [redacted]. This section is being revised to delete [redacted] to Roxane Laboratories, Inc. to package the product in the secondary child-resistant container/closure system. All packaging of the Butorphanol Tartrate Nasal Spray, in the primary and secondary container/closure system, will be performed at Roxane Laboratories, Inc.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products, Roxane Laboratories, Inc. She can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

CENTER FOR DRUG
JAN 18 2002

Elizabeth A. Ernst, R.N., B.S.N.
Associate Director, Regulatory Affairs, DRA-Multisource Products for Roxane Laboratories, Inc.

Telephone (614) 272-4785
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1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Boehringer Ingelheim
Roxane Laboratories

October 8, 2001

Gary Buehler, R. Ph.
Director Office of Generic Drugs
Metro Park North II
7500 Standish Place Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 0 9 2001
OGD

Butorphanol ANDA 75-824

Dear Mr. Buehler,

This letter is in response to a recent inspection of a [redacted], used to [redacted] on Roxane's Butorphanol Nasal Spray. As a result of this inspection, it was recognized that Roxane did not fully comply with FDA's bioequivalence sample retention requirements for in vitro test samples. Roxane is now aware that FDA requires retention of in vitro samples in accordance with the 21 CFR 314.63. While Roxane acknowledges a deviation from FDA expectations in regard to sample retention, substantial documentation exists that verifies that the lots of Roxane drug product specified were used to perform all in vitro tests. Roxane requests that FDA consider the documentation provided. This documentation clearly demonstrates the traceability and accountability of drug product from the lots used for in vitro bioequivalence testing.

Background:

The Division of Scientific Investigations conducted an inspection of [redacted] from 7/23/01 to 7/27/01. This inspection was initiated in response to Roxane Laboratories ANDA 75-824 that was submitted to OGD on 3/25/00.

[redacted] was the [redacted] for Roxane Laboratories required by the Draft Guidance for Industry "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" dated June 1999. At completion of the five day inspection, a Form FDA 483 was issued (see Attachment I). The only deficiency noted by the reviewer was in regard to retention samples for Roxane's Butorphanol Nasal Spray used in the in-vitro testing.

For convenience of review, we have summarized below the historical flow of information and related documents regarding the handling of study drug throughout the testing/study period.

[redacted] conducted the in-vitro bioequivalence testing comparing Roxane's Butorphanol Nasal Spray to Bristol-Myers Squibb's Stadol® NS. The study was performed on the Roxane Product using samples from one lot of drug formulation and three lots of pumps of the test product. The reference product consisted of three lots of Stadol® NS. The lot numbers of the drug products employed in this study are summarized in Table I.

Redacted 2

pages of trade secret and/or confidential commercial information

mistakenly assumed that only compliance with the draft guidance was necessary. Based on the FDA audit, [redacted] many different Sponsors, is recommending and ensuring that they maintain the retention samples for any new and future bioavailability or bioequivalence studies.

In addition, although it is impossible to retroactively assign retention samples, Roxane and [redacted] are willing to have the samples that were originally shipped from [redacted] to Roxane at the conclusion of the study, returned to [redacted] and/or the Agency for verification that these samples are in fact the samples used to conduct the in-vitro testing. After verification, these samples and the test data would be available to the FDA for their review and approval.

This verification process could be accomplished by one or more of the following conditions:

1. Presence of a [redacted] label.
2. Remnants of a [redacted] label, partially removed.
3. Bottle number identification, usually on bottom of the container.
4. Zip-Lock bag with bottle number identification.

[redacted] has an excellent reputation with the industry and thus has no reason, financial or otherwise, to bias the data in any way.

We hope that this correspondence and supporting documentation will provide assurance to the Agency that the in-vitro bioequivalence study was conducted in accordance with the federal regulations. Roxane recognizes that appropriate sample retention procedures were not followed. However, all test products can be accounted for and documentation of custody can be verified by the FDA. Therefore, we believe that after review of this documentation FDA will determine that there is adequate assurance that the product used in the in vitro tests can be appropriately tracked and verified. Roxane requests that FDA determine that adequate assurance of retained samples is available and that ANDA 75-824 can be approved.

If the Agency needs any additional information, please feel free to contact me at 614-272-4785

Respectfully,

Elizabeth Ernst
Associate Director Regulatory Affairs
Roxane Laboratories, Inc.

CC: District Office
DSI
[redacted]

ANDA 75-824

DEC 18 2001

Roxane Laboratories, Inc.
Attention: Shahid Ahmed
P.O. Box 16532
Columbus, OH 43216-6532

Dear Sir:

This is in reference to your abbreviated new drug application dated March 24, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Butorphanol Tartrate Nasal Spray, 2.5 mL (10 mg/mL)

Reference is also made to your amendments dated October 23 and December 18, 2000; May 3, September 19, and October 8 & 23, 2001.

We have completed the review of this abbreviated application and have concluded that this application is deficient and, therefore, not approvable under 21 CFR 314.124 (b)(13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging or holding of the new drug product, Butorphanol Tartrate Nasal Spray by Roxane Laboratories, Inc., comply with current good manufacturing practice (CGMP) regulations.

Our conclusion is based upon the findings revealed during an initial inspection of Roxane Laboratories, Inc. by representatives of the United States Food and Drug Administration from. Upon review of the inspector's report and observations noted during the inspection, we have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time as it can be determined to the Agency that the CGMP-related issues have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved. We note that arrangements are currently being made by the Office of Compliance to reinspect the facility.

You should amend this application when the CGMP-related issues have been satisfactorily resolved. Your amendment to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT.

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. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

12/10/01

for

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

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

N/APA

ORIG AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 2 4 2001
OGD

October 23, 2001

Re: ANDA 75-824
Butorphanol Tartrate Nasal Spray, 10mg/mL
GRATUITOUS AMENDMENT

Dear Mr. Min:

We wish to amend ANDA 75-824. Enclosed please find the hard copy of the amendment which was faxed to Mr. Edwin Ramos today. Per Mr. Ramos' request, this amendment consists of the revised drug product specification for Butorphanol Tartrate Nasal Spray, 10 mg/mL, Specification No. 1472-09. The asterisk on the microbial tests (page 2 of the product specification), indicating that the test will only be performed on the first 3 post-approval batches, for release and stability, and not on annual batches, has been deleted. This means that the microbial tests will be performed on all post approval production batches for release and stability.

Also attached is a copy of the revised stability commitment to reflect this change. The reference to the microbial tests as not required for annual production stability batch in page 4 has been deleted. Testing on the first 3 marketed batches, which refers to the current product specification, was not changed.

As suggested by Mr. Ramos, in the future, we may file a supplement after ANDA approval to delete this test, after we generate data on 10-20 post approval batches.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products, Roxane Laboratories, Inc. She can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.

Elizabeth A. Ernst, R.N., B.S.N.
Associate Director, Regulatory Affairs, DRA-Multisource Products for Roxane Laboratories, Inc.

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Jeen Min

September 19, 2001

ANDA 75-824
Butorphanol Tartrate Nasal Spray, 10 mg/mL

ORIG AMENDMENT
N/AA

GRATUITOUS AMENDMENT

Dear Mr. Min:

We wish to amend ANDA 75-824. Enclosed please find the revised drug product specification for Butorphanol Tartrate Nasal Spray, 10 mg/mL,

[ ]

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products, Roxane Laboratories, Inc. She can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs at (614) 241-4133.

CENTER FOR DRUG EVAL. & RES.
SEP 20 2001

Respectfully,

Elizabeth Ernst
Associate Director, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.

Elizabeth A. Ernst, R.N., B.S.N.
Associate Director, Regulatory Affairs, DRA-Multisource Products for Roxane Laboratories, Inc.

Telephone (614) 272-4785
Telefax (614) 276-2470
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Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AMENDMENT
N/FA

May 3, 2001

Attention: Jeen Min

ANDA 75-824
Butorphanol Tartrate Nasal Spray, 10 mg/mL

FAX AMENDMENT
Chemistry/Labeling Deficiencies

Shahid Ahmed
Vice President, Regulatory Affairs,
DRA-Multisource Products for
Roxane Laboratories, Inc..
Telephone (614) 241-4131
Telefax (614) 276-2470
E-Mail sahmed@cle.boehringer-ingelheim.com

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

Dear Mr. Min:

We wish to amend ANDA 75-824. Enclosed please find a point-by-point response to the questions in the facsimile deficiency letter dated April 19, 2001. This is the hard copy of the amendment telefaxed to you today (see attached confirmation report).

This amendment contains 12 final printed copies of the labeling for your review. Also included is a side-by-side comparison of the final printed labeling based on the Agency's comments in the April 19, 2001 deficiency letter.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products, Roxane Laboratories, Inc. She can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. I can be reached at (614) 241-4131.

Respectfully,

Shahid Ahmed
Vice President, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.

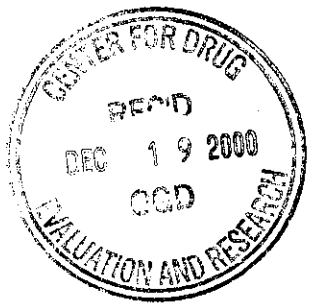
CENTER FOR DRUG EVALUATION AND RESEARCH
MAY 04 2001
CDD

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Dale P. Conner, Pharm.D.
Director, Divison of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT



December 18, 2000

ANDA 75-824
Butorphanol Tartrate Nasal Spray, 10 mg/mL

BIOEQUIVALENCY AMENDMENT

ATTENTION: Krista Scardina, Pharm.D.

Shahid Ahmed
Vice President, Regulatory Affairs,
DRA-Multisource Products for
Roxane Laboratories, Inc.
Telephone 440.232.3320.3333 or
614.241.4131
Telefax 440.232.2772
E-Mail sahmed@cle.boehringer-ingelheim.com

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

Dear Dr. Conner:

We wish to amend ANDA 75-824. Enclosed please find a point-by-point response to the questions in the facsimile deficiency letter dated December 4, 2000. A copy of this letter is attached.

An electronic (diskette) copy of the priming, repriming and tail off test data, as described in the response to Question 3, is provided.

Correspondence concerning this application should be directed to Elizabeth Ernst, Regulatory Affairs and Clinical Research Manager, Roxane Laboratories, Inc. who can be reached at (614) 272-4785 and by telefax at (614) 276-8061. I can be reached at (440) 232-3320, ext. 3333.

Respectfully,

Shahid Ahmed
Vice President, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

NC

November 20, 2000

Attention: Jeen Min

ANDA 75-824
Butorphanol Tartrate Nasal Spray, 10 mg/mL

AMENDMENT – Response to Sample Request for Method Validation

Shahid Ahmed
Vice President, Regulatory Affairs,
DRA-Multisource Products for
Roxane Laboratories, Inc..
Telephone 440.232.3320.3333 or
614.241.4131
Telefax 440.232.2772
E-Mail sahmed@cle.boehringer-ingelheim.com

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

Dear Mr. Min:

We wish to amend ANDA 75-824. Enclosed is a copy of the Amendment to the ANDA for Butorphanol Tartrate Nasal Spray, 10 mg/mL. This is in response to the request by the FDA Philadelphia Laboratory for Butorphanol Tartrate Nasal Spray drug product samples and butorphanol tartrate reference standard for method validation studies.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Regulatory Affairs and Clinical Research Manager, Roxane Laboratories, Inc. who can be reached at (614) 272-4785 and by telefax at (614) 276-8061. I can be reached at (440) 232-3320, ext. 3333.

Respectfully,

Shahid Ahmed
Vice President, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
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Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT

Roxane Laboratories, Inc.

N/A C

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

October 23, 2000

Attention: Jeen Min

ANDA 75-824
Butorphanol Tartrate Nasal Spray, 10 mg/mL

MAJOR AMENDMENT
Chemistry/Labeling Deficiencies

Shahid Ahmed
Vice President, Regulatory Affairs,
DRA-Multisource Products for
Roxane Laboratories, Inc..
Telephone 440.232.3320.3333 or
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Telefax 440.232.2772
E-Mail sahmed@cle.boehringer-ingelheim.com

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

Dear Mr. Min:

We wish to amend ANDA 75-824. Enclosed please find a point-by-point response to the questions in the facsimile deficiency letter dated September 8, 2000.

Please note that included in this amendment is a revision of Section X of the ANDA – Outside Firms Including Contract Testing Laboratories. The revised section is provided in Appendix A of this amendment. This section is being revised to add [redacted] to Roxane Laboratories, Inc.

This amendment contains 4 copies of the revised draft labeling for your review. In addition, also enclosed is a mock-up of the primary and secondary packaging configuration of the Butorphanol Tartrate Nasal Spray container/closure system of the drug product.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to me or Elizabeth Ernst, Regulatory Affairs and Clinical Research Manager, Roxane Laboratories, Inc. I can be reached at (440) 232-3320, ext. 3333 or Elizabeth Ernst can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-8061.

Respectfully,

per

Shahid Ahmed
Vice President, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

April 20, 2000

Sean Alan Reade
Telephone 614-241-4131
Telefax 614-276-0321
E-Mail sreade@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228
Telephone (614) 276-4000
Telefax (614) 274-0974

ANDA No. 75-824
Butorphanol Tartrate Nasal Spray, 10mg/mL
Attention: Saundra Middleton

Re: Authorization Letter from [redacted]
Butorphanol Tartrate Nasal Spray, 10 mg/mL
ANDA No. 75-824

Dear Ms. Middleton,

As requested, enclosed is a hard copy of the authorization letter from [redacted] This letter authorizes [redacted] to represent [redacted] in all matters pertaining to all Drug Master Files submitted by [redacted] A copy of this letter was faxed to your attention on April 13, 2000. Also enclosed, as requested, are three (3) copies of Section XV, Analytical Methods.

Correspondence concerning this application should be directed to Sean Alan F.X. Reade, Director, Drug Regulatory Affairs, Roxane Laboratories, Inc. I can be reached by telephone at (614) 241-4131 and by telefax at (614) 276-0321. In my absence, do not hesitate to contact my colleague, Ms. Virginia Fojas, at (614) 241-4133.

Respectfully,

Sean Alan F.X. Reade, M.A.
Director, Drug Regulatory Affairs
New Drugs and Regulatory Services

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 21 2000
OGD

ANDA 75-824

Roxane Laboratories, Inc.
Attention: Sean Alan F.X. Reade, M.A.
P.O. BOX 16532
Columbus, OH 43216-6532

APR 19 2000

Dear Sir:

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

Reference is also made to the telephone conversation dated April 12, 2000 and your amendment dated April 13, 2000.

NAME OF DRUG: Butorphanol Tartrate Nasal Spray, 10 mg/mL

DATE OF APPLICATION: March 24, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 27, 2000

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:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

/S/

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

Ack for filing
S. Middleton
505(j)(2)(A)
4/13/00

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

March 24, 2000

Sean Alan Reade
Telephone 614-241-4131
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E-Mail sreade@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228
Telephone (614) 276-4000
Telefax (614) 274-0974

Abbreviated New Drug Application
Butorphanol Tartrate Nasal Spray, 10mg/mL

Dear Sir/Madam:

In accordance with 21 CFR 314.94, Roxane Laboratories, Inc. is submitting an Abbreviated New Drug Application (ANDA) for Butorphanol Tartrate Nasal Spray, 10 mg/mL. This ANDA was formatted in accordance with the Guidance for Industry. Organization of an ANDA, February 1999. Additionally, the following guidelines were also used in the preparation of the contents of this ANDA:

- Draft Guidance for Industry. Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products. Chemistry, Manufacturing and Controls Documentation May 1999
- Draft Guidance for Industry. Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, June 1999.

The reference-listed drug is STADOL NS® (butorphanol tartrate) Nasal Spray manufactured by Bristol-Myers Squibb Company. The active ingredient is Butorphanol Tartrate, USP. Roxane Laboratories' Butorphanol Tartrate Nasal Spray, 10 mg/mL (2.5 mL/bottle) and the reference listed drug, STADOL NS® (butorphanol tartrate) Nasal Spray contain the same active and inactive ingredients in the same amounts.

The product will be manufactured, tested, labeled, packaged and released by Roxane Laboratories, Inc. No contract manufacturers or packagers are used.

In accordance with 21 CFR 320.22, Roxane Laboratories, Inc. requests a waiver of the requirements for *in vivo* studies based on demonstration of bioequivalence to the reference-listed drug using *in vitro* tests. The *in vitro* tests are those proposed in the Draft Guidance for Industry. Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, June 1999 referenced above.

1

Boehringer Ingelheim

Re: Abbreviated New Drug Application
Butorphanol Tartrate Nasal Spray, 10mg/mL
March 24, 2000

Copies of correspondences between the Agency and [redacted] acting on behalf of Roxane Laboratories) provided in Section VI, Bioavailability and Bioequivalence Section of this application, confirm that *in vitro* methodology is an acceptable method for demonstrating bioequivalence between Roxane Laboratories' Butophanol Tartrate Nasal Spray, 10 mg/mL and the reference listed drug, STADOL NS® (butorphanol tartrate) Nasal Spray.

Results of the *in vitro* tests, conducted by [redacted], on Roxane Laboratories' Butorphanol Tartrarte Nasal Spray and STADOL NS® (butorphanol tartrate) Nasal Spray are described in the In Vitro Bioequivalence Report provided in Section VI, Bioavailability and Bioequivalence Section, Attachment VIb of this application. Electronic copies of the test reports and bioequivalence workbooks (statistical analyses) are also provided in the appendices to Attachment VIb. Statistical analyses of the data were performed by [redacted], and checked by [redacted]

Sanples and /or a methods validation package will be submitted upon the Office of Generic Drugs' request and direction.

Correspondence concerning this application should be directed to Sean Alan F.X. Reade, Director, Drug Regulatory Affairs, Roxane Laboratories, Inc. I can be reached by telephone at (614) 241-4131 and by telefax at (614) 276-0321. In my absence, do not hesitate to contact my colleague, Ms. Virginia Fojas, at (614) 241-4133.

Respectfully,

Sean Alan F.X. Reade, M.A.
Director, Drug Regulatory Affairs
New Drugs and Regulatory Services