CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-499

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

***Sponsor*:** Apotex Corp.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

APPROVAL LETTER

ANDA 75-499

DEC 4 2002

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

Dear Madam:

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

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

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Butorphanol Tartrate Nasal Spray, 10 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Stadol® NS™ Nasal Spray, 10 mg/mL, of Bristol Myers Squibb Company Pharmaceutical Research Institute).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all

proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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

Sincerely yours,

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

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

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

V:\FIRMSNZ\NOVEX\LTRS&REV\75499apf.doc
F/T by TOH/11/20/02

APPROVAL

comments satisfactory
Lilo Lagos
12/3/02

Robert Powell West
12/4/2002

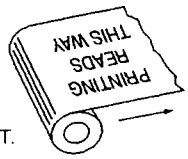
CENTER FOR DRUG EVALUATION AND RESEARCH

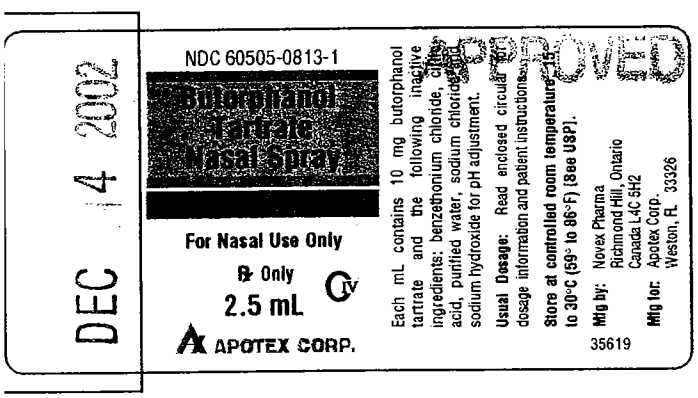
APPLICATION NUMBER:

ANDA 75-499

LABELING

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

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



Enlarged to 150%
By FOIA STAFF

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

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

NDC 60505-0813-1

Butorphanol Tartrate Nasal Spray

[redacted]

For Nasal Use Only

℞ Only C IV

2.5 mL

Bottle and Spray Pump

APOTEX CORP.

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

APPROVED DEC 4 2002

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

Manufactured for:
Apotex Corp.
Weston, FL 33326
130033

UPC Code

128C Bar Code

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-499

LABELING REVIEWS

This review supersedes the review dated April 6, 1999

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

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

Applicant's Name: **Novex Pharma**

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

Labeling Deficiencies:

1. CONTAINER 2.5 mL

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

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

2. PATIENT INSTRUCTIONS

   Satisfactory, in draft.

3. MEDICATION GUIDE

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

4. INSERT

   a. GENERAL COMMENTS

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

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

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

b. TITLE

Include the controlled substance symbol with the title.

c. DESCRIPTION

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

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

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

d. CLINICAL PHARMACOLOGY

i. General Pharmacology and Mechanism of Action, first sentence - Butorphanol is a mixed agonist-antagonist with low intrinsic activity at receptors of the μ-opioid type (morphine-like). It is also an agonist at κ-opioid receptors.

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

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

iv. Pharmacokinetics

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

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

1). Second sentence - ... of butorphanol, with norbutorphanol present at trace levels at most time points. The elimination half life of hydroxybutorphanol is about 18 hours and, as a consequence considerable accumulation (≅ 5-fold) occurs when butorphanol is dosed to steady state (1 mg transnasally q6h for 5 days).

2). Delete the last sentence.

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

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

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

vi. Postoperative

A). Retitle this "Postoperative Pain".

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

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

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

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

viii. Individualization of Dosage

A). Delete the first and third paragraphs.

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

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

e. WARNINGS

Add the following subsections after the second paragraph:

Drug Abuse and Dependence

Drug Abuse

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

Physical Dependence, Tolerance and Withdrawal

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

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

DEPENDENCE section below).

f. PRECAUTIONS

i. Hepatic and Renal Disease

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

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

iii. Use in Ambulatory Patients

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

B). Revise this subsection as follows:

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

iv. Drug Interactions

A). Add the following as the second paragraph:

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

6 mg subcutaneous dose of sumatriptan.

B). Add the following as the third paragraph:

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

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

v. Information for Patients

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

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

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

vi. Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

vii. Pregnancy -

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

B). First paragraph, third sentence -

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

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

viii. Labor and Delivery, first paragraph

A). First sentence

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

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

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

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

x. Geriatric Use

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

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

g. ADVERSE REACTIONS

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

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

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

iv. Fourth paragraph

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

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

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

D). Delete [redacted]

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

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

vii. Delete [redacted]
(two instances)

viii. Paragraph beginning "The following infrequent ...

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

ix. Cardiovascular - chest pain, hypertension, tachycardia

x. Nervous - Delete [redacted].

xi. Respiratory - Delete [redacted].

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

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

h. DRUG ABUSE AND DEPENDENCE

Revise this section as follows:

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

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

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

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

Postmarketing Experience

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

i. OVERDOSAGE

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

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

iii. Add the following as the last paragraph:

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

j. DOSAGE AND ADMINISTRATION

i. Decrease the prominence of the subsection headings.

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

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

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

v. Labor - Delete the first paragraph.

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

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

k. HOW SUPPLIED

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

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

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

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

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

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

Attachments: Innovator approval letter and MEDICATION GUIDE

Copy of Reference Listed Drug labeling removed.

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

Do you have 12 Final Printed Labels and Labeling?

Container Labels:

Patient Instructions:

Medication Guide:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-890

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

NDA Firm: Bristol-Myers Squibb

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

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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

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

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

NOTES/QUESTIONS TO THE CHEMIST:

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

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

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

FOR THE RECORD:

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

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

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

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

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

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

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

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

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

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

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

Primary Reviewer: Adolph Vezza Date:

A. Vezza 5/25/99

Team Leader: Charlie Hoppes Date:

5/25/99

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cc:

ANDA: 75-499
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/4/2/99|V:\FIRMSNZ\NOVEX\LTRS&REV\75499na1.L.doc
Review

APPEARS THIS WAY
ON ORIGINAL

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

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

Applicant's Name: **Novex Pharma**

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

Labeling Deficiencies:

1. CARTON

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

2. PATIENT INSTRUCTIONS

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

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

3. MEDICATION GUIDE

   a. See comment above under (a) PATIENT INSTRUCTIONS

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

   c. Boxed Statements – First item, second sentence:

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

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

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

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

      Delete ——————— ".

4. INSERT

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

   b. DESCRIPTION

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

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

c. CLINICAL PHARMACOLOGY

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

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

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

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

d. PRECAUTIONS (Labor and Delivery)

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

e. HOW SUPPLIED

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

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

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

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

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

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

Do you have 12 Final Printed Labels and Labeling?

Container Labels:

Patient Instructions:

Medication Guide:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-890

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

NDA Firm: Bristol-Myers Squibb

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

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels:

Other Comments:

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

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

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

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

FOR THE RECORD:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Applicant's Name: **Novex Pharma**

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

Labeling Deficiencies:

1. GENERAL

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

2. CONTAINER

   a. See general comment above.

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

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

3. CARTON

   a. See general comment above.

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

      2.5 mL Bottle and Spray Pump

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

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

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

         Dispense with patient instructions and medication guide.

4. PATIENT INSTRUCTIONS

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

5. MEDICATION GUIDE

   See comment above under PATIENT INSTRUCTIONS.

6. INSERT

   a. See general comment above.

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

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

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

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

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

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

Copy of Reference Listed Drug labeling removed.

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

Do you have 12 Final Printed Labels and Labeling?

Container Labels:

Patient Instructions:

Medication Guide:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-890

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

NDA Firm: Bristol-Myers Squibb

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

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels:

Other Comments:

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

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

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

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

FOR THE RECORD:

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

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

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