

Approval Date: APR 20 2007

FREEDOM OF INFORMATION SUMMARY

**ORIGINAL ABBREVIATED NEW ANIMAL
DRUG APPLICATION**

ANADA 200-408

Butorphanol Tartrate Injection (2 mg/mL)

Indicated for the relief of pain in cats caused by major or minor
trauma, or pain associated with surgical procedures

Sponsored by:

IVX Animal Health, Inc.

2007-200-408

FOIS 1

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

- a. File Number: ANADA 200-408
- b. Sponsor: IVX Animal Health, Inc.
3915 South 48th Street Ter.
St. Joseph, MO 64503
- Drug Labeler Code: 059130
- c. Established Name: Butorphanol tartrate
- d. Proprietary Name: Butorphanol Tartrate Injection (2mg/mL)
- e. Dosage Form: Injection
- f. How Supplied: 10 mL vials
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: Each mL contains 2 mg butorphanol base (as butorphanol tartrate, USP)
- i. Route of Administration: Subcutaneous injection
- j. Species/Class: Cats
- k. Recommended Dosage: 0.4 mg of butorphanol per kilogram body weight (0.2 mg/lb)
- l. Pharmacological Category: Analgesic
- m. Indications: Indicated for the relief of pain in cats caused by major or minor trauma, or pain associated with surgical procedures.
- n. Pioneer Product: TORBUGESIC-SA; butorphanol tartrate; NADA 141-047; Fort Dodge Animal Health, Division of Wyeth.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

Ordinarily, the ANADA sponsor is required to show that the generic product is bioequivalent to the pioneer, which has been shown to be safe and effective. If bioequivalence is demonstrated through a clinical endpoint study, then a tissue residue study to establish the withdrawal time for the generic product should also be conducted. For certain dosage forms, the agency will grant a waiver from the requirement of an *in vivo* bioequivalence study (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guideline, October 9, 2002).

Based on the formulation characteristics of the generic product, IVX Animal Health, Inc. was granted a waiver from the requirement for an *in vivo* bioequivalence study for the generic product Butorphanol Tartrate Injection (2 mg/mL). The generic product is administered as an injection, contains the same active ingredient in the same concentration and dosage form as the pioneer product, and contains no inactive ingredients that may significantly affect the absorption of the active ingredient. The pioneer product, TORBUGESIC-SA (butorphanol tartrate), the subject of Fort Dodge Animal Health, Division of Wyeth, NADA 141-047, was approved on July 5, 1994.

3. HUMAN SAFETY:

This drug is intended for use in cats, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

Human Warnings are provided on the product label as follows: **“NOT FOR HUMAN USE.”**

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b)(2) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that Butorphanol Tartrate Injection (2mg/mL) when used under its proposed conditions of use, is safe and effective for its labeled indications.

5. ATTACHMENTS:

Facsimile generic labeling and currently approved pioneer labeling are attached as follows:

Generic Labeling for ANADA 200-408:

Butorphanol Tartrate Injection (2mg/mL) – Bottle label - 10 mL
Butorphanol Tartrate Injection (2mg/mL) – Bottle Outsert - 10 mL
Butorphanol Tartrate Injection (2mg/mL) – Shipping Label - 4 x 25 x 10 mL

Pioneer Labeling for NADA 141-047

Butorphanol Tartrate (2mg/mL) – Bottle Label, actual size
Butorphanol Tartrate (2mg/mL) – Package Insert - 10 mL
Butorphanol Tartrate (2mg/mL) – Shipping Label

<p>NDC 59130-779-10 NET CONTENTS: 10 mL Butorphanol Tartrate Injection (2 mg/mL) Contains 2 mg butorphanol base per mL as butorphanol tartrate, USP</p> <p>CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.</p> <p>U.S. Patent 4,812,111 Approved by FDA</p> <p>Lot No. _____ Exp. Date _____</p> 	<p>Veterinary Injection For Use in Cats Only NOT FOR HUMAN USE Read Package Insert.</p> <p>Each mL of solution contains:</p> <table border="0"> <tr><td>Butorphanol base (as butorphanol tartrate, USP).....</td><td>2.0 mg</td></tr> <tr><td>Citric acid, USP</td><td>3.3 mg</td></tr> <tr><td>Sodium citrate, USP</td><td>6.4 mg</td></tr> <tr><td>Sodium chloride, USP</td><td>4.7 mg</td></tr> <tr><td>Benzethonium chloride, USP</td><td>0.1 mg</td></tr> <tr><td>Water for injection, USP</td><td>q.s</td></tr> </table> <p>DOSAGE: By subcutaneous injection. Cats: Analgesic dose 0.4 mg/kg (0.2 mg/lb) body weight. Repeat up to 4 times per day as required. Do not treat for more than 2 days.</p> <p>Store between 15° and 30°C (59° and 86°F).</p> <p>Manufactured by IVX Animal Health, Inc. St. Joseph, MO 64503 AmTech® is a registered trademark of IVX Animal Health, Inc. 600120-10 C-ISS1106</p>	Butorphanol base (as butorphanol tartrate, USP).....	2.0 mg	Citric acid, USP	3.3 mg	Sodium citrate, USP	6.4 mg	Sodium chloride, USP	4.7 mg	Benzethonium chloride, USP	0.1 mg	Water for injection, USP	q.s
Butorphanol base (as butorphanol tartrate, USP).....	2.0 mg												
Citric acid, USP	3.3 mg												
Sodium citrate, USP	6.4 mg												
Sodium chloride, USP	4.7 mg												
Benzethonium chloride, USP	0.1 mg												
Water for injection, USP	q.s												

Label size 1.25" x 3.5"

Butorphanol 
Tartrate Injection
(2 mg/mL)
Veterinary Injection
For Use In Cats Only

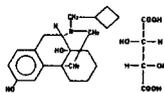
Caution

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description

Butorphanol tartrate, USP is a synthetic, centrally acting, narcotic agonist-antagonist analgesic with potent anti-tussive activity. The results from laboratory and clinical studies suggest the existence of several distinct types of receptors that are responsible for the activity of opioid and opioid-like drugs. When activated, the μ (mu)-receptors are involved in analgesia, respiratory depression, miosis, physical dependence and feelings of well-being (euphoria). When activated, the κ (kappa)-receptors are involved in analgesia, as well as less intense (as compared to μ -receptors) miosis and respiratory depression. Butorphanol is considered to be a weak antagonist at the μ -receptor, but a strong agonist at the κ -receptor. Thus, butorphanol provides analgesia with a lower incidence and/or intensity of adverse reactions (e.g., miosis and respiratory depression) than traditional opioids. Butorphanol tartrate is a member of the phenanthrene series. The chemical name is Morphinan-3, 14-diol, 17-(cyclobutylmethyl)-, (-)-, (S-(R*, R*))-2,3-dihydroxybutanediate (1:1) (salt). It is a white, crystalline, water soluble substance having a molecular weight of 477.55; its molecular formula is $C_{21}H_{28}NO_6 \cdot C_4H_8O_6$.

Chemical Structure:



Each mL of Butorphanol Tartrate Injection contains 2 mg butorphanol base (as butorphanol tartrate, USP); 3.3 mg citric acid, USP; 6.4 mg sodium citrate, USP; 4.7 mg sodium chloride, USP; and 0.1 mg benzethonium chloride, USP; q.s. with water for injection, USP.

Clinical Pharmacology

Feline Pharmacology

The magnitude and duration of analgesic activity of butorphanol were studied in cats under controlled laboratory conditions using both a visceral pain model and a somatic pain model.^{1,2} Subcutaneous butorphanol dosages of 0.4 mg/kg produced analgesia significantly ($p < 0.05$) greater than the placebo for up to two hours in the somatic pain model. At the label dose (0.4 mg/kg), cardiopulmonary depressant effects were minimal after treatment with butorphanol as demonstrated in cats.^{1,2}

Clinical studies confirmed the analgesic effect of butorphanol administered subcutaneously in the cat. In field trials the overall analgesic effect was rated as satisfactory in approximately 75% of butorphanol treated cats. The duration of activity in cats responding to butorphanol ranged from 15 minutes to 8 hours. However, in 70% of responding cats the duration of activity was 3 to 6 hours following subcutaneous administration.

Safety Studies in Cats

Daily subcutaneous injections of butorphanol in cats, beginning at a dosage of 2 mg/kg the first week and doubling each week to a final dosage of 16 mg/kg on the fourth week resulted in no deaths. No evidence of toxicity was observed during the first three weeks of the experiment, other than pain on injection. During the fourth week, transient incoordination, salivation, or mild seizures were observed within the first hour in the cats following the 16 mg/kg dosage (40 times the recommended clinical dosage). No other clinical, serum chemistry, or gross necropsy evidence of drug toxicity was encountered in any of the cats.

In subacute safety studies butorphanol was injected subcutaneously to each of six cats at dosages of 0 (saline), 0.4, 1.2 or 2.0 mg/kg, every six hours for six days and continued once daily for a total of 21 days. The only adverse clinical effect observed was pain on injection. Histopathologic changes indicative of minimal to slight irritation were noted at the injection sites in 3 of 6 cats in the low dose group, 4 to 6 cats in the middle dose group and 6 of 6 cats in the high dose group. Histopathologic changes of focal renal tubular dilation were noted in half of the cats in the high dose group.

Indications

Butorphanol Tartrate Injection is indicated for the relief of pain in cats caused by major or minor trauma, or pain associated with surgical procedures.

Warning(s)

NOT FOR HUMAN USE.

Precautions

Butorphanol Tartrate Injection, a potent analgesic, should be used with caution with other sedative or analgesic drugs as these are likely to produce additive effects.

Safety for use in pregnant female cats, breeding male cats or kittens less than 4 months of age has not been determined. Use of Butorphanol Tartrate Injection can therefore not be recommended in these groups.

Adverse Reactions

In clinical trials in cats, pain on injection, mydriasis, disorientation, swallowing / licking and sedation were reported.

Dosage

The recommended dosage in cats is 0.4 mg of butorphanol per kilogram body weight (0.2 mg/lb) given by subcutaneous injection. This is equivalent to 1.0 mL of Butorphanol Tartrate Injection per 10 lbs of body weight.

Pre-clinical model studies and clinical field trials in cats demonstrated that the analgesic effects of Butorphanol Tartrate Injection are seen within 20 minutes and persist in the majority of responding cats for 3 to 6 hours following subcutaneous injection (see Feline Pharmacology). The dose may be repeated up to 4 times per day for up to 2 days.

Supply

10 mL vials Butorphanol Tartrate Injection, 2 mg base activity per mL.

For Use In Cats Only

Store between 15° and 30°C (59° and 86°F).

References

- Sawyer, D.C. and Rech, R.H. "Analgesia and Behavioral Effects of Butorphanol, Nalbuphine and Pentazocine in the Cat." *J. Amer. Hosp. Assoc.* 23: 438-446, 1987.
- Mandsager, R.E. and Raffé, M.R. "Evaluation of Periosteal Nociception in the Cat." *PVN* 2(4): 237-242, 1991.

600120-10 C-ISS1106

Manufactured by
 IVX Animal Health, Inc.
 St. Joseph, MO 64503

Job #12898

Manufacturing Information
 Product Name: Butorphanol Tartrate Injection
 Strength: 2 mg/mL
 Formulation: Sterile, Aqueous Solution
 Container: 10 mL Vial
 Lot: 600120-10
 Date: 10/15/98
 Expiration: 10/15/03
 Storage: Store at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F).
 Distribution: Distributed by IVX Animal Health, Inc., St. Joseph, MO 64503.
 © 1998 IVX Animal Health, Inc. All rights reserved.
 This product is a registered trademark of IVX Animal Health, Inc.
 12898

**Butorphanol Tartrate
Injection (2.0 mg/mL)**

4 x 25 x 10 mL

LOT NO: ?????? EXP: ????

Store between 15°C-30°C (59°F-86°F)

IVX Animal Health, Inc.

St. Joseph, MO 64503

**Butorphanol Tartrate
Injection (2.0 mg/mL)**

4 x 25 x 10 mL

LOT NO: ?????? EXP: ????

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IVX Animal Health, Inc.

St. Joseph, MO 64503

**Butorphanol Tartrate
Injection (2.0 mg/mL)**

4 x 25 x 10 mL

LOT NO: ?????? EXP: ????

Store between 15°C-30°C (59°F-86°F)

IVX Animal Health, Inc.

St. Joseph, MO 64503

NDC 0856-4531-01

Torbugesic-SA® (IV)
BUTORPHANOL
TARTRATE, USP

Fort Dodge
Veterinary Injection
contains 2 mg
butorphanol base per mL as
butorphanol tartrate, USP
10 mL

CAUTION: Federal law restricts this drug to use
by or on the order of a licensed veterinarian.
NADA 141 047, Approved by FDA

Each mL of solution contains:
Butorphanol base
Butorphanol tartrate, USP 2.0 mg
Ethacrynic acid, USP 2.0 mg
Sodium chloride, USP 8.4 mg
Sodium chloride, USP 4.7 mg
Strychnine chloride, USP 0.1 mg
Water for injection, USP q.s.

READ PACKAGE INSERT.

NOT FOR HUMAN USE.

DOSAGE: By subcutaneous injection. Calculate
Ampgesic dose 0.4 mg/kg (0.2 mg/lb) body
weight. Repeat up to 4 times per day as required.
Do not treat for more than 2 days.
Store at controlled room temperature 15° to 30°C
(59° to 86°F).

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

4531C
90420



US
For Sale



SAMPLE

Torbugesic-SA®
BUTORPHANOL TARTRATE, USP
 Veterinary Injection

IV

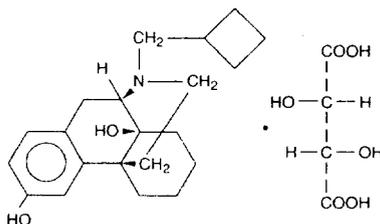
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DESCRIPTION

Butorphanol tartrate, USP is a synthetic, centrally acting, narcotic agonist-antagonist analgesic with potent antitussive activity. The results from laboratory and clinical studies suggest the existence of several distinct types of receptors that are responsible for the activity of opioid and opioid-like drugs. When activated, the μ (mu)-receptors are involved in analgesia, respiratory depression, miosis, physical dependence and feelings of well-being (euphoria). When activated, the κ (kappa)-receptors are involved in analgesia, as well as less intense (as compared to μ -receptors) miosis and respiratory depression. Butorphanol is considered to be a weak antagonist at the μ -receptor, but a strong agonist at the κ -receptor. Thus, butorphanol provides analgesia with a lower incidence and/or intensity of adverse reactions (e.g., miosis and respiratory depression) than traditional opioids.

Butorphanol tartrate is a member of the phenanthrene series. The chemical name is Morphinan-3, 14-diol, 17-(cyclobutylmethyl)-, (-)-, (S- (R*, R*))- 2,3-dihydroxybutanedioate (1:1) (salt). It is a white, crystalline, water soluble substance having a molecular weight of 477.55; its molecular formula is $C_{21}H_{29}NO_2 \cdot C_4H_6O_6$.

Chemical Structure:

Each mL of TORBUGESIC-SA contains 2 mg butorphanol base (as butorphanol tartrate, USP); 3.3 mg citric acid, USP; 6.4 mg sodium citrate, USP; 4.7 mg sodium chloride, USP; and 0.1 mg benzethonium chloride, USP; q.s. with water for injection, USP.

CLINICAL PHARMACOLOGY**Feline Pharmacology**

The magnitude and duration of analgesic activity of butorphanol were studied in cats under controlled laboratory conditions using both a visceral pain model and a somatic pain model.^{1,2} Subcutaneous butorphanol dosages of 0.4 mg/kg produced analgesia significantly ($p < 0.05$) greater than the placebo for up to two hours in the somatic pain model. At the label dose (0.4 mg/kg), cardiopulmonary depressant effects were minimal after treatment with butorphanol as demonstrated in cats.^{1,2}

Clinical studies confirmed the analgesic effect of butorphanol administered subcutaneously in the cat. In field trials the overall analgesic effect was rated as satisfactory in approximately 75% of butorphanol treated cats. The duration of activity in cats responding to butorphanol ranged from 15 minutes to 8 hours. However, in 70% of responding cats the duration of activity was 3 to 6 hours following subcutaneous administration.

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and doubling each week to a final dosage of 16 mg/kg on the fourth week, resulted in no deaths. No evidence of toxicity was observed during the first three weeks of the experiment, other than pain on injection. During the fourth week, transient incoordination, salivation, or mild seizures were observed within the first hour in the cats following the 16 mg/kg dosage (40 times the recommended clinical dosage). No other clinical, serum chemistry, or gross necropsy evidence of drug toxicity was encountered in any of the cats.

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INDICATIONS

TORBUGESIC-SA (butorphanol tartrate, USP) is indicated for the relief of pain in cats caused by major or minor trauma, or pain associated with surgical procedures.

WARNINGS

NOT FOR HUMAN USE.

PRECAUTIONS

TORBUGESIC-SA, a potent analgesic, should be used with caution with other sedative or analgesic drugs as these are likely to produce additive effects.

Safety for use in pregnant female cats, breeding male cats or kittens less than 4 months of age has not been determined. Use of TORBUGESIC-SA can therefore not be recommended in these groups.

ADVERSE REACTIONS

In clinical trials in cats, pain on injection, mydriasis, disorientation, swallowing/licking and sedation were reported.

DOSAGE

The recommended dosage in cats is 0.4 mg of butorphanol per kilogram body weight (0.2 mg/lb) given by subcutaneous injection. This is equivalent to 1.0 mL of TORBUGESIC-SA per 10 lbs of body weight.

Pre-clinical model studies and clinical field trials in cats demonstrated that the analgesic effects of TORBUGESIC-SA are seen within 20 minutes and persist in the majority of responding cats for 3 to 6 hours following subcutaneous injection (see **Feline Pharmacology**). The dose may be repeated up to 4 times per day for up to 2 days.

SUPPLY

10 mL vials TORBUGESIC-SA (butorphanol tartrate, USP) Veterinary Injection, 2 mg base activity per mL.

NDC 0856-4531-01 — 10 mL — vials

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

REFERENCES

1. Sawyer, D.C. and Rech, R.H. "Analgesia and Behavioral Effects of Butorphanol, Nalbuphine and Pentazocine in the Cat," *J. Amer. Hosp. Assoc.* 23: 438-446, 1987.
2. Mandsager, R.E. and Raffe, M.R. "Evaluation of Periosteal Nociception in the Cat," *PVN* 2(4): 237-242, 1991.

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

AMERICAN HOME PRODUCTS CORPORATION

Subsidiary:

FORT DODGE ANIMAL HEALTH

P. O. Box 518

Fort Dodge, Iowa 50501

U. S. Vet. License No. 112

00033

TORBUGESIC SA

24 - 10 mL RSC Shipper Label (B4532G)

April 2001

RES. NO. 304531

B4532G
????

RESOURCE #



304531

24 - 10 ML

STORE AT CONTROLLED ROOM
TEMPERATURE 15° TO 30°C
59° TO 86°F)

SAMPLE

LOT



???????????????

LOT

???????????????

QTY



24

UPC



726287145325

EXP. DATE

???????

FORT DODGE ANIMAL HEALTH
FORT DODGE, IOWA 50501 USA

AMERICAN HOME PRODUCTS CORPORATION
by Ana Hoban
12 Apr 01