HFA-305

Date of Approval: JAN 22 2003

FREEDOM OF INFORMATION (FOI) SUMMARY

Butorphanol Tartrate Injection

For relief of pain associated with colic in adult horses and yearlings

ANADA 200-322

Phoenix Scientific, Inc.

3915 South 48th Street Terrace

St. Joseph, MO 64503

FOI S 1

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION

ANADA 200-322

ANADA/GENERIC SPONSOR:
Phoenix Scientific, Inc.
3915 South 48th Street Terrace, St. Joseph, MO 64503

a.	**Established Name:**	Butorphanol Tartrate, USP
b.	**Trade Name/Proprietary Name:**	Butorphanol Tartrate Injection
c.	**Dosage Form:**	Injection
d.	**How Supplied:**	10 mL & 50 mL Type I amber glass bottles
e.	**How Dispensed:**	Rx;Schedule IV(CIV)
f.	**Amount of Active Ingredients**	10 mg butorphanol /mL
g.	**Route of Administration:**	Intravenous Injection
h.	**Species:**	Equine
i.	**Pioneer Product**	Torbugesic® (Butorphanol Tartrate) NADA 135-780

INDICATIONS FOR USE: Butorphanol Tartrate Injection is indicated for the relief of pain associated with colic in adult horses and yearlings.

RECOMMENDED DOSAGE: The recommended dosage in the horse is 0.1 mg of butorphanol per kilogram of body weight, (0.05 mg/lb) by intravenous injection. This is equivalent to 5 mL of Butorphanol Tartrate Injection for each 1000 lbs body weight. The dose may be repeated within 3 to 4 hours but treatment should not exceed 48 hours.

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 shows 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 end-point 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 Guidance, October 2000).

Based upon the formulation characteristics of the generic product, Phoenix Scientific was granted a waiver from the requirement for an *in vivo* bioequivalence study for the generic product, Butorphanol Tartrate. The generic product is administered as an injectable dosage form, 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, the subject of Fort Dodge Animal Health's NADA 135-780, was approved on June 11, 1985.

3. HUMAN SAFETY:

None required as the product is intended for use in horses only. The labeling contains the statement "Warning: Not to be used in horses intended for food."

Human Safety Relative to Possession, Handling and Administration: Labeling contains adequate caution/warning statements. Butorphanal tartrate is a Schedule IV drug; Rx only.

4. AGENCY CONCLUSIONS:

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

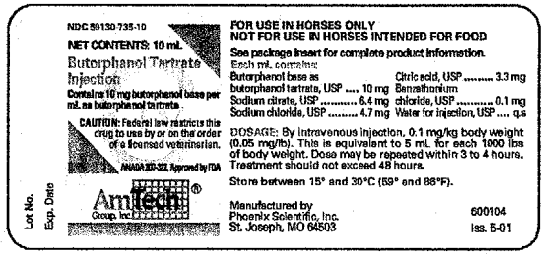
5. ATTACHMENTS:

The following **generic** labeling and currently approved **pioneer** labeling are attached.

Generic Labeling

1. Facsimile package labeling for generic product; 10 mL and 50 mL and package insert.

Pioneer Labeling	2	Pioneer package labeling for Torbugesic®; 10 mL and 50 mL and package insert.



NDC 59130-735-10

NET CONTENTS: 10 mL

Butorphanol Tartrate Injection

Contains 10 mg butorphanol base per mL as butorphanol tartrate.

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

ANADA 200-322, Approved by FDA

AmTech® Group, Inc.

Lot No.

Exp. Date

FOR USE IN HORSES ONLY
NOT FOR USE IN HORSES INTENDED FOR FOOD

See package insert for complete product information.

Each mL contains:

Butorphanol base as butorphanol tartrate, USP .... 10 mg
Sodium citrate, USP ..... 6.4 mg
Sodium chloride, USP ..... 4.7 mg
Citric acid, USP ..... 3.3 mg
Benzethonium chloride, USP ..... 0.1 mg
Water for injection, USP .... q.s

DOSAGE: By intravenous injection, 0.1 mg/kg body weight (0.05 mg/lb). This is equivalent to 5 mL for each 1000 lbs of body weight. Dose may be repeated within 3 to 4 hours. Treatment should not exceed 48 hours.

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

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503

600104
Iss. 5-01

NDC 59130-735-10

NET CONTENTS: 10 mL

Butorphanol Tartrate Injection

Contains 10 mg butorphanol base per mL as butorphanol tartrate.

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

ANADA 200-322, Approved by FDA

AmTech® Group, Inc.

Lot No.

Exp. Date

FOR USE IN HORSES ONLY
NOT FOR USE IN HORSES INTENDED FOR FOOD

See package insert for complete product information.

Each mL contains:

Butorphanol base as butorphanol tartrate, USP .... 10 mg
Sodium citrate, USP ..... 6.4 mg
Sodium chloride, USP ..... 4.7 mg
Citric acid, USP ..... 3.3 mg
Benzethonium chloride, USP ..... 0.1 mg
Water for injection, USP .... q.s

DOSAGE: By intravenous injection, 0.1 mg/kg body weight (0.05 mg/lb). This is equivalent to 5 mL for each 1000 lbs of body weight. Dose may be repeated within 3 to 4 hours. Treatment should not exceed 48 hours.

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

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503

600104
Iss. 5-01

200%

8

NDC 59130-735-11
NET CONTENTS: 50 mL
Butorphanol Tartrate Injection
Contains 10 mg butorphanol base per mL as butorphanol tartrate
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
FOR USE IN HORSES ONLY
NOT FOR USE IN HORSES INTENDED FOR FOOD
ANADA 200-XXX, Approved by FDA
AmTech® Group, Inc.

Lot No.
Exp. Date

See package insert for complete product information.
Each mL contains: Butorphanol base as butorphanol tartrate, USP ..... 10 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.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
DOSAGE: By intravenous injection, 0.1 mg/kg body weight (0.05 mg/lb). This is equivalent to 5 mL for each 1000 lbs of body weight. Dose may be repeated within 3 to 4 hours. Treatment should not exceed 48 hours.

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503
600104 Iss. 7-00

3 59130 73511 6

OPEN HERE

28807 amtech 133-2400 8/2/00 black 1797

IV

NDC 59130-735-11
NET CONTENTS: 50 mL
Butorphanol Tartrate Injection
Contains 10 mg butorphanol base per mL as butorphanol tartrate
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
FOR USE IN HORSES ONLY
NOT FOR USE IN HORSES INTENDED FOR FOOD
ANADA 200-XXX, Approved by FDA
AmTech® Group, Inc.

Lot No.
Exp. Date

See package insert for complete product information.
Each mL contains: Butorphanol base as butorphanol tartrate, USP ..... 10 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.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
DOSAGE: By intravenous injection, 0.1 mg/kg body weight (0.05 mg/lb). This is equivalent to 5 mL for each 1000 lbs of body weight. Dose may be repeated within 3 to 4 hours. Treatment should not exceed 48 hours.

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503
600104 Iss. 7-00

3 59130 73511 6

OPEN HERE

28807 amtech 133-2400 8/2/00 black 1797

CUSTOMER PROOF • CHECK CAREFULLY!

Customer: PHOENIX SCIENTIFIC P.O. #: STEPHANIE

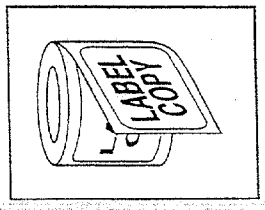
CYREL #: 28807 (ts) Date Sent: 8/3/00 8/15/00 8/31/00

LABEL: amtech UNWIND #: 4

SIZE: 1.375 x 4.5

VARNISH: ☐ YES ☐ NO ☐ PATTERN ☐ FLOOD

COLORS: black 1797 red



Fax Proofs are intended for proofing of content and placement only, not for exact size or color breaks.

Every effort has been taken to insure the accuracy and conformance to applicable regulations on this proof. However, please check carefully as the final liability rests with the customer.

Approved by: _____ Date approved: _____

AM

ANADA 200-XXX, Approved by FDA

BUTORPHANOL TARTRATE INJECTION

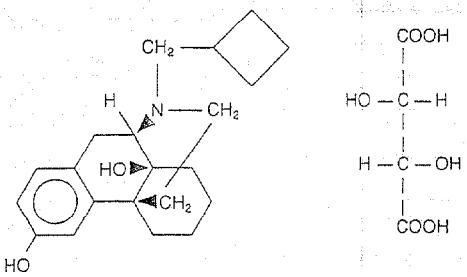
CAUTION

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

DESCRIPTION

Butorphanol Tartrate Injection is a totally synthetic, centrally acting, narcotic agonist-antagonist analgesic with potent antitussive activity. It 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 Butorphanol Tartrate Injection contains 10 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

Comparative Pharmacology

In animals, butorphanol has been demonstrated to be 4 to 30 times more potent than morphine and pentazocine (Talwin®-V) respectively.[1] In humans, butorphanol has been shown to have 5-7 times the analgesic activity of morphine and 20 times that of pentazocine.[2,3] Butorphanol has 15 to 20 times the oral antitussive activity of codeine or dextromethorphan in dogs and guinea pigs. [4]

As an antagonist, butorphanol is approximately equivalent to nalorphine and 30 times more potent than pentazocine.[1]

Cardiopulmonary depressant effects are minimal after treatment with butorphanol as demonstrated in dogs[5], humans[6,7] and horses.[8] Unlike classical narcotic agonist analgesics which are associated with decreases in blood pressure, reduction in heart rate and concomitant release of histamine, butorphanol does not cause histamine release.[1] Furthermore, the cardiopulmonary effects of butorphanol are not distinctly dosage-related but rather reach a ceiling effect beyond which further dosage increases result in relatively lesser effects.

Reproduction: Studies performed in mice and rabbits revealed no evidence of impaired fertility or harm to the fetus due to butorphanol tartrate. In the female rat, parenteral administration was associated with increased nervousness and decreased care for the newborn, resulting in a decreased survival rate of the newborn. This nervousness was seen only in the rat species.

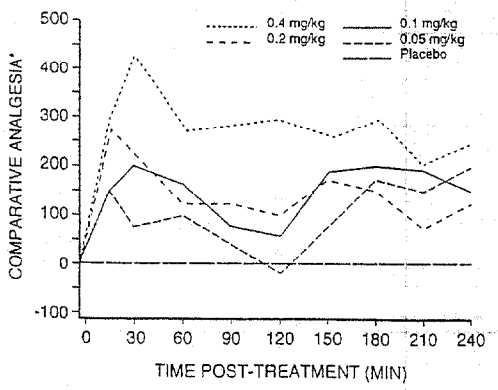
Equine Pharmacology

Following intravenous injection in horses, butorphanol is largely eliminated from the blood within 3 to 4 hours. The drug is extensively metabolized in the liver and excreted in the urine.

In ponies, butorphanol given intramuscularly at a dosage of 0.22 mg/kg, was shown to alleviate experimentally induced visceral pain for about 4 hours.[9]

In horses, intravenous dosages of butorphanol ranging from 0.05 to 0.4 mg/kg were shown to be effective in alleviating visceral and superficial pain for at least 4 hours, as illustrated in the following figure:

Analgesic Effects of Butorphanol Given at Various Dosages in Horses with Abdominal Pain



*Pain threshold in butorphanol-treated colicky horses relative to placebo controls.

A definite dosage-response relationship was detected in that butorphanol dosage of 0.1 mg/kg was more effective than 0.05 mg/kg but not different from 0.2 mg/kg in alleviating deep abdominal pain.

Acute Equine Studies

Rapid intravenous administration of butorphanol at a dosage of 2 mg/kg (20 times the recommended dosage) to a previously unmedicated horse resulted in a brief episode of inability to stand, muscle fasciculation, a convulsive seizure of 6 seconds duration and recovery within three minutes. The same dosage administered after 10 successive daily 1 mg/kg dosages of butorphanol resulted only in transient sedative effects. During the 10-day course of administration at 1 mg/kg (10 times the recommended use level) in two horses, the only detectable drug effects were transient behavioral changes typical of narcotic agonist activity. These included muscle fasciculation about the head and neck, dysphoria, lateral nystagmus, ataxia and salivation. Repeated administration of butorphanol at 1 mg/kg (10 times the recommended dose) every four hours for 48 hours caused constipation in one of two horses.

Subacute Equine Studies

Horses were found to tolerate butorphanol given intravenously at dosages of 0.1, 0.3 and 0.5 mg/kg every 4 hours for 48 hours followed by once daily injections for total of 21 days. The only detectable drug effects were slight transient ataxia observed occasionally in the high dosage group. No clinical, laboratory, or gross or histopathologic evidence of any butorphanol related toxicity was encountered in the horses.

INDICATIONS

Butorphanol Tartrate Injection is indicated for the relief of pain associated with colic in adult horses and yearlings. Clinical studies in the horse have show that Butorphanol Tartrate Injection alleviates abdominal pain associated with torsion, impaction, intussusception, spasmodic and tympanic colic and postpartum pain.

WARNINGS

NOT FOR USE IN HORSES INTENDED FOR FOOD.
NOT FOR HUMAN USE.

CAUTION

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.

There are no well-controlled studies using butorphanol in breeding horses, weanlings and foals. Therefore, the drug should not be used in these groups.

ADVERSE REACTIONS

In clinical trials in horses, the most commonly observed side effect was slight ataxia which lasted 3 to 10 minutes. Marked ataxia was reported in 1.5% of the 327 horses treated. Mild sedation was reported in 9% of the horses.

DOSAGE

The recommended dosage in the horse is 0.1 mg of butorphanol per kilogram of body weight, (0.05 mg/lb) by intravenous injection. This is equivalent to 5 mL of Butorphanol Tartrate Injection for each 1000 lbs body weight. The dose may be repeated within 3 to 4 hours but treatment should not exceed 48 hours. Pre-clinical model studies and clinical field trials in horses demonstrate that the analgesic effects of Butorphanol Tartrate Injection are seen within 15 minutes following injection and persist for about 4 hours.

HOW SUPPLIED

50 mL vials Butorphanol Tartrate Injection. 10 mg base activity per mL.
10 mL vials Butorphanol Tartrate Injection. 10 mg base activity per mL.

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

REFERENCES

1. Pircio, A.W. *et al:* "The Pharmacology of Butorphanol." *Arch. Int. Pharmacodyn. Ther.* 220 2): 231-257, 1976.
2. Dobkin, A.B. *et al:* "Butorphanol and Pentazocine in Patients with Severe Post-operative Pain." *Clin. Pharmacol. Ther.* 18: 547-553, 1975.
3. Gilbert, M.S. *et al:* "Intramuscular Butorphanol and Meperidine in Postoperative Pain." *Clin. Pharmacol. Ther.* 20:359-364, 1976.
4. Cavanagh, R.L. *et al:* "Antitussive Properties of Butorphanol." *Arch. Int. Pharmacodyn. Ther.* 220 (2): 258-268, 1976.
5. Schurig, J.E. *et al:* "Effect of Butorphanol and Morphine on Pulmonary Mechanics, Arterial Blood Pressure, and Venous Plasma Histamine in the Anesthetized Dog." *Arch. Int. Pharmacodyn. Ther.* 233: 296-304, 1978.
6. Nagashmina, H. *et al:* "Respiratory and Circulatory Effects of Intravenous Butorphanol and Morphine." *Clin. Pharmacol. Ther.* 19: 735-745, 1976.
7. Popio, K.A. *et al:* "Hemodynamic and Respiratory Effects of Morphine and Butorphanol." *Clin. Pharmacol. Ther.* 23: 281-287, 1978.
8. Robertson, J.T. and Muit, W.W.: "Cardiopulmonary Effects of Butorphanol Tartrate in Horses." *Am. J. Vet. Res.* 42: 41-44. 1981.
9. Kalpravidh, M. *et al:* "Effects of Butorphanol, Flunixin, Levorphanol, Morphine, Pentazocine and Xylazine in Ponies." *Am. J. Vet. Res.* 45: 217-223, 1984.

Manufactured By:
Phoenix Scientific, Inc.
St. Joseph, MO 64503

600104 Iss. 7-00

See package insert for complete product information.

Each mL contains: Butorphanol base as butorphanol tartrate, USP ..... 10 mg
Citric acid, USP ..... 6.4 mg
Sodium citrate, USP ..... 3.3 mg
Sodium chloride, USP ..... 4.7 mg
Benzethonium chloride, USP ..... 0.1 mg
Water for injection, USP ..... q.s.

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

DOSAGE: By intravenous injection, 0.1 mg/kg body weight (0.05 mg/lb). This is equivalent to 5 mL for each 1000 lbs of body weight. Dose may be repeated within 3 to 4 hours. Treatment should not exceed 48 hours.

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503

600104 Iss. 7-00

3 591307351116

ANADA 200-XXX, Approved by FDA

BUTORPHANOL TARTRATE INJECTION

IV

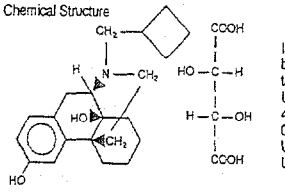
CAUTION

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

DESCRIPTION

Butorphanol Tartrate Injection is a totally synthetic, centrally acting, narcotic agonist-antagonist analgesic with potent antitussive activity. It 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 Butorphanol Tar
Injection contains 10
butorphanol base (as butorph
tartrate, USP), 3.3 mg citric
USP, 6.4 mg sodium citrate, U
4.7 mg sodium chloride, USP,
0.1 mg benzethonium chlo
USP, q.s. with water for injec
USP.

CLINICAL PHARMACOLOGY

Comparative Pharmacology

In animals, butorphanol has been demonstrated to be 4 to 30 times more potent

morphine and pentazocine (Talwin®-V) respectively.[1] In humans, butorphanol has been shown to have 5-7 times the analgesic activity of morphine and 20 times that of pentazocine.[2,3] Butorphanol has 15 to 20 times the oral antitussive activity of codeine or dextromethorphan in dogs and guinea pigs.[4]

As an antagonist, butorphanol is approximately equivalent to nalorphine and 30 times more potent that pentazocine.[1]

Cardiopulmonary depressant effects are minimal after treatment with butorphanol as demonstrated in dogs[5], humans[6,7] and horses.[8] Unlike classical narcotic agonist analgesics which are associated with decreases in blood pressure, reduction in heart rate and concomitant release of histamine, butorphanol does not cause histamine release.[1] Furthermore, the cardiopulmonary effects of butorphanol are not distinctly dosage-related but rather reach a ceiling effect beyond which further dosage increases result in relatively lesser effects.

Reproduction: Studies performed in mice and rabbits revealed no evidence of impaired fertility or harm to the fetus due to butorphanol tartrate. In the female rat,

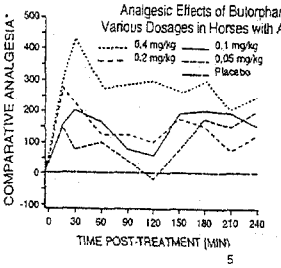
parenteral administration was associated with increased nervousness and decreased care for the newborn, resulting in a decreased survival rate of the newborn. This nervousness was seen only in the rat species.

Equine Pharmacology

Following intravenous injection in horses, butorphanol is largely eliminated from the blood within 3 to 4 hours. The drug is extensively metabolized in the liver and excreted in the urine.

In ponies, butorphanol given intramuscularly at a dosage of 0.22 mg/kg, was shown to alleviate experimentally induced visceral pain for about 4 hours.[9]

In horses, intravenous dosages of butorphanol ranging from 0.05 to 0.4 mg/kg were shown to be effective in alleviating visceral and superficial pain for at least 4 hours, as illustrated in the following figure:



*Pain threshold in butorph
treated colicky horses relat
placebo controls.

A definite dosage-resp
relationship was detected i
butorphanol dosage of
mg/kg was more effective
0.05 mg/kg but not different
0.2 mg/kg in alleviating
abdominal pain.

Acute Equine Studies

Rapid intravenous administration of butorphanol at a dosage of 2 mg/kg (20 times the recommended dosage) to a previously unmedicated horse resulted in a brief episode of inability to stand, muscle fasciculation, a convulsive seizure of 6 seconds duration and recovery within three minutes. The same dosage administered after 10 successive daily 1 mg/kg dosages of butorphanol resulted only in transient sedative effects. During the 10-day course of administration at 1 mg/kg (10 times the recommended use level) in two horses, the only detectable drug effects were transient behavioral changes typical of narcotic agonist activity. These included muscle fasciculation about the head and neck, dysphoria, lateral nystagmus, ataxia and salivation. Repeated administration of butorphanol at 1 mg/kg (10 times the recommended dose) every four hours for 48 hours caused constipation in one of two horses.

Subacute Equine Studies

Horses were found to tolerate butorphanol given intravenously at dosages of 0.1, 0.3

and 0.5 mg/kg every 4 hours for 48 hours followed by once daily injections for a total of 21 days. The only detectable drug effects were slight transient ataxia observed occasionally in the high dosage group. No clinical, laboratory, or gross or histopathologic evidence of any butorphanol related toxicity was encountered in the horses.

INDICATIONS

Butorphanol Tartrate Injection is indicated for the relief of pain associated with colic in adult horses and yearlings. Clinical studies in the horse have shown that Butorphanol Tartrate Injection alleviates abdominal pain associated with torsion, impaction, intussusception, spasmodic and tympanic colic and postpartum pain.

WARNING

NOT FOR USE IN HORSES INTENDED FOR FOOD. NOT FOR HUMAN USE.

CAUTION

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

There are no well-controlled studies using butorphanol in breeding horses, weani and foals. Therefore, the drug should not be used in these groups.

ADVERSE REACTIONS

In clinical trials in horses, the most commonly observed side effect was slight at which lasted 3 to 10 minutes. Marked ataxia was reported in 1.5% of the 327 hor treated. Mild sedation was reported in 9% of the horses.

DOSAGE

The recommended dosage in the horse is 0.1 mg of butorphanol per kilogram body weight, (0.05 mg/lb) by intravenous injection. This is equivalent to 5 mL Butorphanol Tartrate Injection for each 1000 lbs body weight. The dose may

repeated within 3 to 4 hours but treatment should not exceed 48 hours. Pre-clinical model studies and clinical field trials in horses demonstrate that the analgesic effects of Butorphanol Tartrate Injection are seen within 15 minutes following injection and persist for about 4 hours.

HOW SUPPLIED

50 mL vials Butorphanol Tartrate Injection. 10 mg base activity per mL.
10 mL vials Butorphanol Tartrate Injection. 10 mg base activity per mL.

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

REFERENCES

1. Pircio, A.W. *et al:* "The Pharmacology of Butorphanol." *Arch. Int. Pharmacodyn. Ther.* 220 (2): 231-257. 1976.
2. Dobkin, A.B. *et al:* "Butorphanol and Pentazocine in Patients with Severe Post-

operative Pain." *Clin. Pharmacol. Ther.* 18: 547-553. 1975.
3. Gilbert, M.S. *et al:* "Intramuscular Butorphanol and Meperidine in Postoperative Pain." *Clin. Pharmacol. Ther.* 20:359-364. 1976.
4. Cavanagh, R.L. *et al:* "Antitussive Properties of Butorphanol." *Arch. Int. Pharmacodyn. Ther.* 220 2): 258-268. 1976.
5. Schurig, J.E. *et al:* "Effect of Butorphanol and Morphine on Pulmonary Mechanics, Arterial Blood Pressure, and Venous Plasma Histamine in the Anesthetized Dog." *Arch. Int. Pharmacodyn. Ther.* 233: 296-304. 1978.
6. Nagashmina, H. *et al:* "Respiratory and Circulatory Effects of Intravenous Butorphanol and Morphine." *Clin. Pharmacol. Ther.* 19: 735-745. 1976.
7. Popio, K.A. *et al:* "Hemodynamic and Respiratory Effects of Morphine and Butorphanol." *Clin. Pharmacol. Ther.* 23: 281-287. 1978.
8. Robertson, J.T. and Muir, W.W.: "Cardiopulmonary Effects of Butorphanol Tartrate in Horses." *Am. J. Vet. Res.* 42: 41-44. 1981.

9. Kalpravidh, M. *et al:* "Effects of Butorphanol, Flunixin, Levorphanol, Morph Pentazocine and Xylazine in Ponies." *Am. J. Vet. Res.* 45: 217-223. 1984.

Manufactured By:
Phoenix Scientific, Inc.
St. Joseph, MO 64503

600104 Iss. 7

NADA 135-780, Approved by FDA

FORT DODGE®

Torbugesic®

BUTORPHANOL TARTRATE

Veterinary Injection

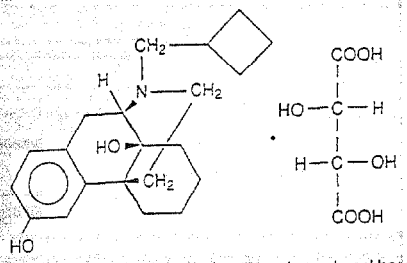
CAUTION

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

DESCRIPTION

TORBUGESIC (butorphanol tartrate) is a totally synthetic, centrally acting, narcotic agonist-antagonist analgesic with potent antitussive activity. It 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 contains 10 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

Comparative Pharmacology

In animals, butorphanol has been demonstrated to be 4 to 30 times more potent than morphine and pentazocine (Talwin®-V) respectively.[1] In humans, butorphanol has been shown to have 5 to 7 times the analgesic activity of morphine and 20 times that of pentazocine.[2,3] Butorphanol has 15 to 20 times the oral antitussive activity of codeine or dextromethorphan in dogs and guinea pigs.[4]

As an antagonist, butorphanol is approximately equivalent to nalorphine and 30 times more potent than pentazocine.[1]

Cardiopulmonary depressant effects are minimal after treatment with butorphanol as demonstrated in dogs[5], humans[6,7] and horses.[8] Unlike classical narcotic agonist analgesics which are associated with decreases in blood pressure, reduction in heart rate and concomitant release of histamine, butorphanol does not cause histamine release.[1] Furthermore, the cardiopulmonary effects of butorphanol are not distinctly dosage-related but rather reach a ceiling effect beyond which further dosage increases result in relatively lesser effects.

Reproduction: Studies performed in mice and rabbits revealed no evidence of impaired fertility or harm to the fetus due to butorphanol tartrate. In the female rat, parenteral administration was associated with increased nervousness and decreased care for the newborn, resulting in a decreased survival rate of the newborn. This nervousness was seen only in the rat species.

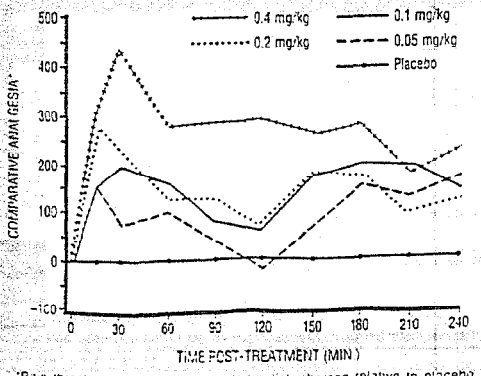
Equine Pharmacology

Following intravenous injection in horses, butorphanol is largely eliminated from the blood within 3 to 4 hours. The drug is extensively metabolized in the liver and excreted in the urine.

In ponies, butorphanol given intramuscularly at a dosage of 0.22 mg/kg, was shown to alleviate experimentally induced visceral pain for about 4 hours.[9]

In horses, intravenous dosages of butorphanol ranging from 0.05 to 0.4 mg/kg were shown to be effective in alleviating visceral and superficial pain for at least 4 hours, as illustrated in the following figure:

Analgesic Effects of Butorphanol Given at Various Dosages in Horses with Abdominal Pain



*Pain threshold in butorphanol-treated colicky horses relative to placebo controls

A definite dosage-response relationship was detected in that butorphanol dosage of 0.1 mg/kg was more effective than 0.05 mg/kg but not different from 0.2 mg/kg in alleviating deep abdominal pain.

Acute Equine Studies

Rapid intravenous administration of butorphanol at a dosage of 2 mg/kg (20 times the recommended dosage) to a previously unmedicated horse resulted in a brief episode of inability to stand, muscle fasciculation, a convulsive seizure of 6 seconds duration and recovery within three minutes. The same dosage administered after 10 successive daily 1 mg/kg dosages of butorphanol resulted only in transient sedative effects. During the 10-day course of administration at 1 mg/kg (10 times the recommended use level) in two horses, the only detectable drug effects were transient behavioral changes typical of narcotic agonist activity. These included muscle fasciculation about the head and neck, dysphoria, lateral nystagmus, ataxia and salivation. Repeated administration of butorphanol at 1 mg/kg (10 times the recommended dose) every four hours for 48 hours caused constipation in one of two horses.

Subacute Equine Studies

Horses were found to tolerate butorphanol given intravenously at dosages of 0.1, 0.3 and 0.5 mg/kg every 4 hours for 48 hours followed by once daily injections for a total of 21 days. The only detectable drug effects were slight transient ataxia observed occasionally in the high dosage group. No clinical, laboratory, or gross or histopathologic evidence of any butorphanol-related toxicity was encountered in the horses.

INDICATIONS

TORBUGESIC (butorphanol tartrate) is indicated for the relief of pain associated with colic in adult horses and yearlings. Clinical studies in the horse have shown that TORBUGESIC alleviates abdominal pain associated with torsion, impaction, intussusception, spasmodic and tympanic colic and postpartum pain.

WARNINGS

NOT FOR USE IN HORSES INTENDED FOR FOOD. NOT FOR HUMAN USE.

CAUTION

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

There are no well-controlled studies using butorphanol in breeding horses, weanlings and foals. Therefore, the drug should not be used in these groups.

ADVERSE REACTIONS

In clinical trials in horses, the most commonly observed side effect was slight ataxia which lasted 3 to 10 minutes. Marked ataxia was reported in 1.5% of the 327 horses treated. Mild sedation was reported in 9% of the horses.

DOSAGE

The recommended dosage in the horse is 0.1 mg of butorphanol per kilogram of body weight (0.05 mg/lb) by intravenous injection. This is equivalent to 5 mL of TORBUGESIC for each 1000 lbs body weight. The dose may be repeated within 3 to 4 hours but treatment should not exceed 48 hours. Pre-clinical model studies and clinical field trials in horses demonstrate that the analgesic effects of TORBUGESIC are seen within 15 minutes following injection and persist for about 4 hours.

HOW SUPPLIED

50 mL vials TORBUGESIC (butorphanol tartrate) Veterinary Injection, 10 mg base activity per mL.

NDC 0856-2033-20 — 50 mL — vials

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

NDC 0856-2036-20 — 10 mL — vials

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

REFERENCES

1. Pircio, A.W. *et al:* "The Pharmacology of Butorphanol," *Arch. Int. Pharmacodyn. Ther.* 220 (2): 231–257, 1976.
2. Dobkin, A.B. *et al:* "Butorphanol and Pentazocine in Patients with Severe Postoperative Pain," *Clin. Pharmacol. Ther.* 18: 547–553, 1975.
3. Gilbert, M.S. *et al:* "Intramuscular Butorphanol and Meperidine in Postoperative Pain," *Clin. Pharmacol. Ther.* 20: 359–364, 1976.
4. Cavanagh, R.L. *et al:* "Antitussive Properties of Butorphanol," *Arch. Int. Pharmacodyn. Ther.* 220 (2): 258–268, 1976.
5. Schurig, J.E. *et al:* "Effect of Butorphanol and Morphine on Pulmonary Mechanics, Arterial Blood Pressure, and Venous Plasma Histamine in the Anesthetized Dog," *Arch. Int. Pharmacodyn. Ther.* 233: 296–304, 1978.
6. Nagashmina, H. *et al:* "Respiratory and Circulatory Effects of Intravenous Butorphanol and Morphine," *Clin. Pharmacol. Ther.* 19: 735–745, 1976.
7. Popio, K.A. *et al:* "Hemodynamic and Respiratory Effects of Morphine and Butorphanol," *Clin. Pharmacol. Ther.* 23: 281–287, 1978.
8. Robertson, J.T. and Muir, W.W.: "Cardiopulmonary Effects of Butorphanol Tartrate in Horses," *Am. J. Vet. Res.* 42: 41–44, 1981.
9. Kalpravidh, M. *et al:* "Effects of Butorphanol, Flunixin, Levorphanol, Morphine, Pentazocine and Xylazine in Ponies," *Am. J. Vet. Res.* 45: 217–223, 1984.

Fort Dodge Laboratories, Inc.
Fort Dodge, Iowa 50501 USA

91105 Rev. January 1995 4640E

NDC 0856-2033-20

Torbugesic®

BUTORPHANOL TARTRATE

FOR USE IN HORSES ONLY

NOT FOR USE IN HORSES INTENDED FOR FOOD

Each mL of solution contains:

Butorphanol base as butorphanol tartrate, USP	10 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.

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

FORT DODGE®

Veterinary Injection

contains 10 mg butorphanol base per mL as butorphanol tartrate

50 mL

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

NADA 135-780, Approved by FDA

READ PACKAGE INSERT

DOSAGE: By intravenous injection, 0.1 mg/kg body weight (0.05 mg/lb). This is equivalent to 5 mL for each 1000 lbs of body weight. Dose may be repeated within 3 to 4 hours. Treatment should not exceed 48 hours.

Fort Dodge Laboratories, Inc.
Fort Dodge, Iowa 50501 USA

Lot 454181

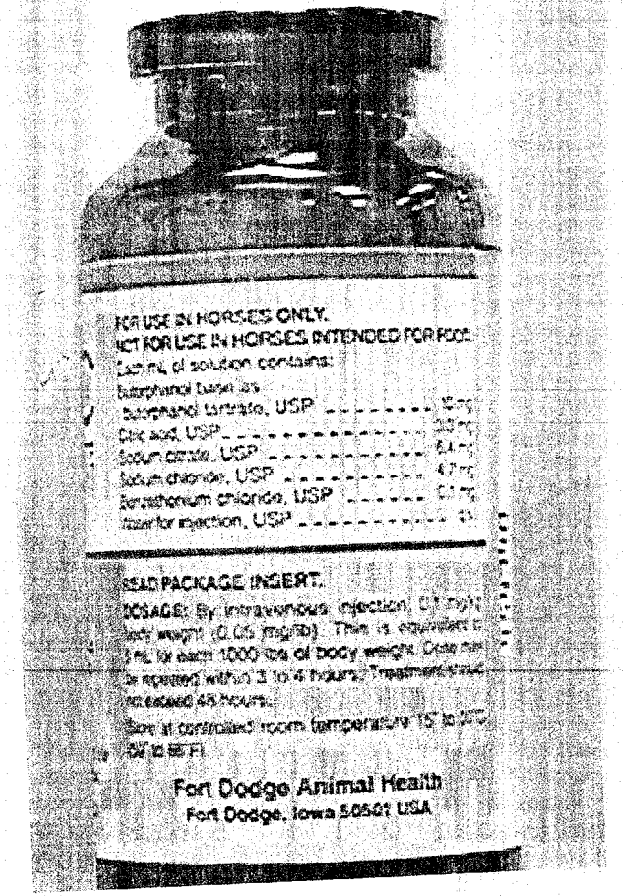
Exp. Date JUL 99

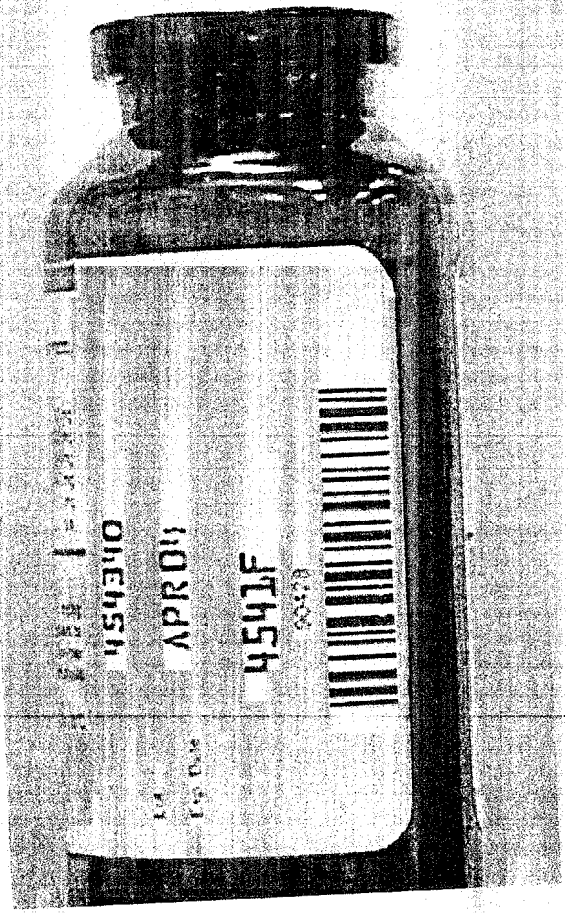
4542F

91105

24

NDC 0856-2033-10
Torbugesic® CIV
BUTORPHANOL TARTRATE
Veterinary Injection
Fort Dodge
contains 10 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 135-780, Approved by FDA


FOR USE IN HORSES ONLY.
NOT FOR USE IN HORSES INTENDED FOR FOOD
Each mL of solution contains:
butorphanol base as
butorphanol tartrate, USP
Citric acid, USP
Sodium citrate, USP
Sodium chloride, USP
Benzethonium chloride, USP
Water for injection, USP
READ PACKAGE INSERT.
DOSAGE: By intravenous injection, 0.1 mg/kg body weight (0.05 mg/lb). This is equivalent to 1 mL for each 1000 lbs of body weight. Dose may be repeated within 3 to 4 hours. Treatment should not exceed 48 hours.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA


APR 01
Exp Date