

DOLOREX- butorphanol tartrate injection
Merck Sharp & Dohme Corp.

DOLOREX®
(BUTORPHANOL TARTRATE)

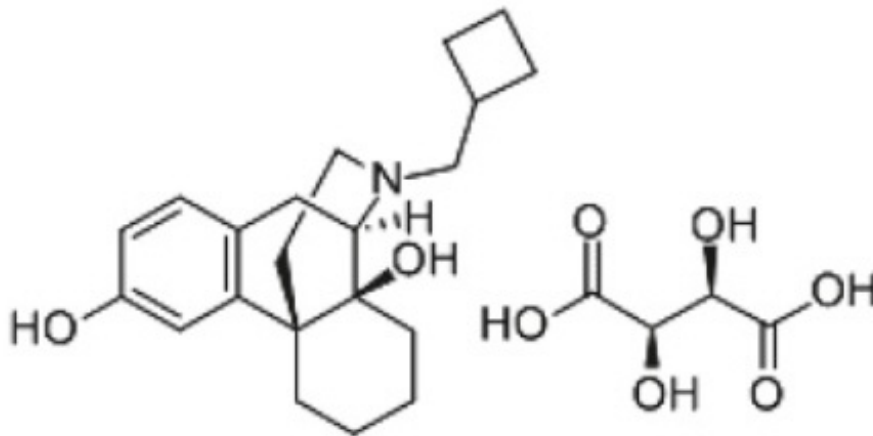
CIV

CAUTION

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

DESCRIPTION

DOLOREX (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 C₂₁H₂₉NO₂ C₄H₆O₆.



Each mL of DOLOREX contains 10 mg butorphanol base (as butorphanol tartrate, USP), 3.3 mg citric acid, Ph.Eur., 6.4 mg sodium citrate, Ph.Eur., 4.7 mg sodium chloride, Ph.Eur., and 0.1 mg benzethonium chloride, Ph.Eur., q.s. with water for injection, Ph.Eur.

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 dogs⁵, 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.

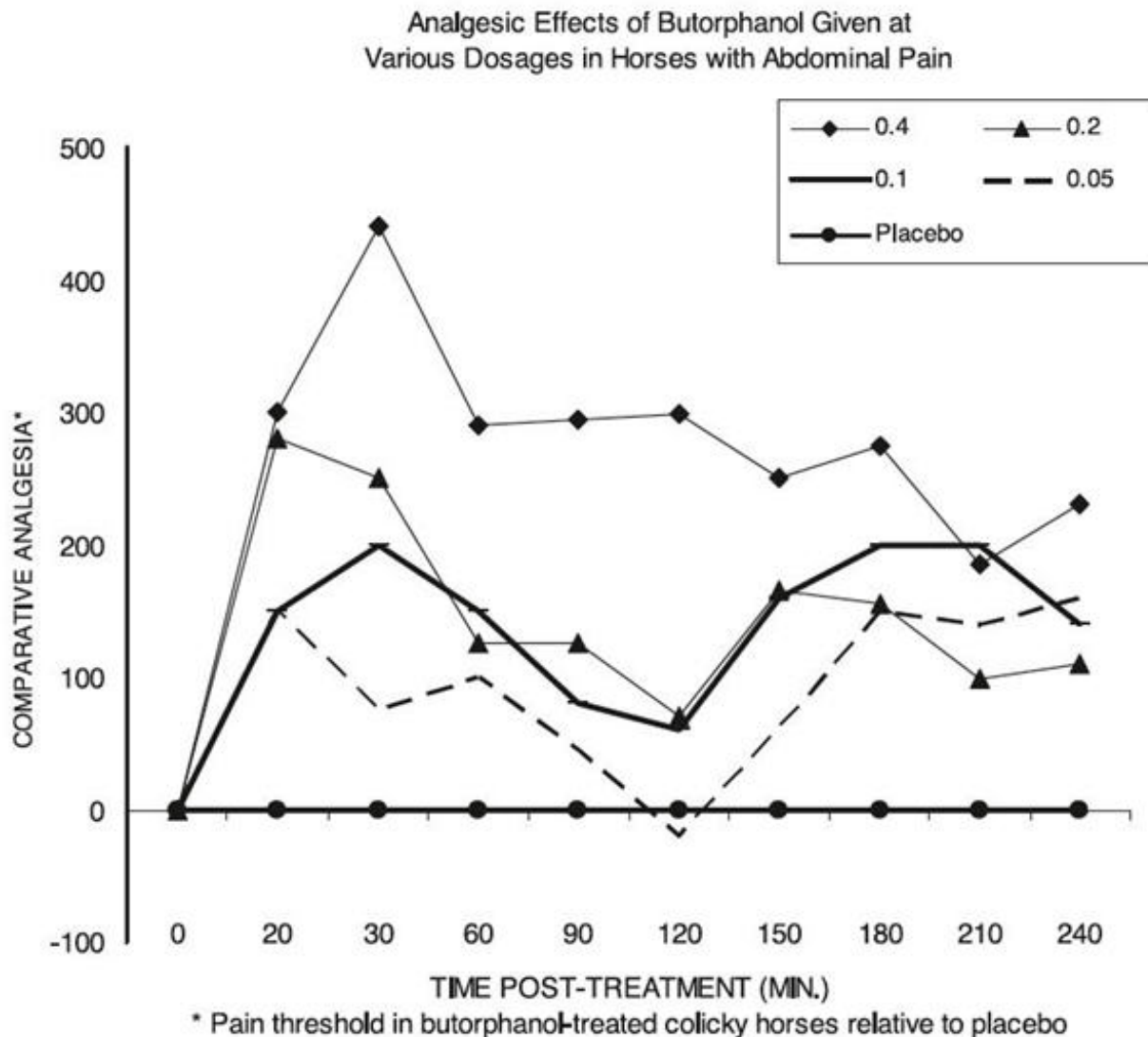
Reproduction studies performed in mice and rabbits revealed no evidence of impaired fertility or harm to the fetus due to butorphanol tartrate. In the female rat, parenteral administration was associated with increased nervousness and decreased care for newborn, resulting in a decreased survival rate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



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 2.0 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 3 minutes. The same

dosage administered after 10 successive daily 1.0 mg/kg dosages of butorphanol resulted only in transient sedative effects. During the 10 day course of administration at 1.0 mg/kg (10 times the recommended use level) in 2 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 1.0 mg/kg (10 times the recommended dosage) every 4 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

DOLOREX (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 butorphanol tartrate alleviates abdominal pain associated with torsion, impaction, intussusception, spasmodic and tympanic colic, and postpartum pain.

WARNING

FOR USE IN HORSES ONLY. NOT FOR USE IN HORSES INTENDED FOR HUMAN CONSUMPTION.

CAUTION

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

HOW SUPPLIED

DOLOREX is supplied in 50 mL vials (Order Code No. 017070).

Store at or below 25°C (77°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. Shurig, 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 Pharm Ther* 19:735-745, 1976.
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8. Robertson, J.T. and W.W. Muir. 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.

Intervet Inc d/b/a Merck Animal Health
Summit, NJ 07901 12/11

By:
INTERVET INTERNATIONAL GmbH, Unterschleissheim - Germany

ANADA 200 - 239, APPROVED BY FDA
088614 R3

PRINCIPAL DISPLAY PANEL - 50 mL Vial Carton

MERCK
Animal Health

CIV

dolorex®
(butorphanol tartrate)

50 mL



DOLOREX

butorphanol tartrate injection

Product Information

| | | | |
|--------------------------------|--------------------------|---------------------------|---------------|
| Product Type | PRESCRIPTION ANIMAL DRUG | Item Code (Source) | NDC:57926-722 |
| Route of Administration | INTRAVENOUS | DEA Schedule | CIV |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|-------------------|---------------|
| Butorphanol Tartrate (UNII: 2L7I72RUHN) (Butorphanol - UNII:QV897JC36D) | Butorphanol | 10 mg in 1 mL |

Inactive Ingredients

| Ingredient Name | Strength |
|---|----------|
| Citric Acid Monohydrate (UNII: 2968PHW8QP) | |
| Sodium Citrate (UNII: 1Q73Q2JULR) | |
| Sodium Chloride (UNII: 451W47IQ8X) | |
| Benzethonium Chloride (UNII: PH41D05744) | |
| Water (UNII: 059QF0KO0R) | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|---------------------|----------------------|--------------------|
| 1 | NDC:57926-722-66 | 1 in 1 CARTON | | |
| 1 | | 50 mL in 1 VIAL | | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANADA | ANADA200239 | 06/22/2012 | |

Labeler - Merck Sharp & Dohme Corp. (001317601)

Establishment

| Name | Address | ID/FEI | Business Operations |
|-----------------------------|---------|-----------|---------------------|
| Intervet International GMBH | | 328855635 | MANUFACTURE |

Establishment

| Name | Address | ID/FEI | Business Operations |
|-----------------------------|---------|-----------|---------------------|
| TEVA Czech Industries s.r.o | | 643896244 | API MANUFACTURE |

Revised: 7/2012

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