

NOV 9, 2001

Approval letter dated: _____

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

ANADA 200-124

FLUXININ MEGLUMINE INJECTION

For the control of pyrexia associated with bovine respiratory disease and endotoxemia. Flunixin Meglumine Injection is also indicated for the control of inflammation in endotoxemia

Sponsored by:

Phoenix Scientific, Inc.
3915 South 48th Street Terrace
St. Joseph, MO 64503-0457

FOIS 1

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

- a. Generic Name: flunixin meglumine injection
- b. Trade Name: FLUNIXIN MEGLUMINE INJECTION
- c. Dosage Form: Injectable Solution
- d. How Supplied: 100 & 250 ml vials
- e. How Dispensed: Rx
- f. Amount of Active Ingredients: 50 mg/mL
- g. Route of Administration: Intravenous (Horses & Cattle)
Intramuscular (Horses)
- h. Species: Horses and cattle (new)
- i. Pioneer Product BANAMINE[®] Injectable Solution
NADA 101-479, Schering-Plough

Effect of Supplement: The supplement provides revised labeling with the addition of a new species, cattle, to the previously approved generic product for horses only.

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 (53 FR 50460, December 15, 1988, First GADPTRA Policy Letter) an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). Phoenix Scientific, Inc. is supplementing their ANADA for the addition of cattle claims.

Based upon the formulation characteristics of the generic product, Phoenix Scientific, Inc. was granted a waiver on April 15, 1992, from conducting an *in vivo* bioequivalence study with flunixin meglumine solution. The generic product was approved on September 25, 1995, for use in horses only,

The three-year exclusivity period for the cattle claims granted to the pioneer product ended on May 5, 2001. Phoenix Scientific is supplementing their approved generic product for the addition of the cattle claims. No new data was required for the addition of the cattle claims.

3. **HUMAN FOOD SAFETY**

The acceptable daily intake (ADI), tolerance, target tissue, and withdrawal period are the same for the pioneer and generic products:

21 CFR 556.286: ADI is 0.72 micrograms/kg/day. A tolerance is established for parent flunixin free acid of 0.125 ppm in liver (target tissue) and 0.025 ppm in cattle muscle,

Withdrawal: 4 days

4. **AGENCY CONCLUSION:**

This is a Supplemental Abbreviated New Animal Drug Application (ANADA) filed under section 512(b)(2) of the Federal Food, Drug, and Cosmetic (FFD&C) Act. The Supplement provides for the addition of cattle claims to the previously approved horse claims. The exclusivity period granted to the pioneer for cattle claims ended on May 5, 2001.

Bioequivalence of this generic animal drug, FLUNIXIN MEGLUMINE INJECTION (50 mg/mL), to the pioneer product, Schering Plough's BANAMINE[®] Injectable Solution (NADA 101-479), was established by demonstration of chemical equivalence. The original generic animal drug was approved on September 25, 1995, for use in horses only.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)(v)(vii)), this is a Category II change providing for the addition of new therapeutic claims in cattle. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Attachment: .

Generic facsimile labeling: 100 mL vial
250 mL vial
Package insert

Pioneer labeling: 100 mL vial
Package insert

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, Md 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 827-6500.

INDICATIONS: Horses: Flunixin Meglumine Injection is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also recommended for the alleviation of visceral pain associated with colic in the horse.

Cattle: Flunixin Meglumine Injection is indicated for the control of pyrexia associated with bovine respiratory disease and endotoxemia. Flunixin Meglumine Injection is also indicated for the control of inflammation in endotoxemia.

Read accompanying directions carefully.

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

Lot No. _____
Exp. Date _____

NDC 59130-643-01
NET CONTENTS: 100 mL
FLUNIXIN MEGGLUMINE
INJECTION 50 mg/mL

For Intravenous or Intramuscular Use in Horses and for Intravenous Use in Beef and Nonlactating Dairy Cattle Only. Not for Use in Lactating or Dry Dairy Cows. Not for Use in Veal Calves.

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

FOR ANIMAL USE ONLY
KEEP OUT OF REACH OF CHILDREN
ANADA 200-124, APPROVED BY FDA

AmTech
Group, Inc.

Each milliliter contains:
Flunixin Meglumine equivalent to
Flunixin 50 mg
Edetate Disodium 0.1 mg
Sodium Formaldehyde
Sulfoxylate 2.5 mg
Diethanolamine 4.0 mg
Propylene Glycol 207.2 mg
Phenol (as preservative) ... 5.0 mg
Water For Injection q.s.
with hydrochloric acid to adjust pH

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within four days of the last treatment. Not for use in lactating or dry dairy cows. A withdrawal period has not been established for this product in preparturient calves. Do not use in calves to be processed for veal. Not for use in horses intended for food.

Store between 2° and 39°C (36° and 96°F).

600052 Rev. 11-00

3 59130 64301 5

INDICATIONS: Horse: Flunixin Meglumine Injection is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also recommended for the alleviation of visceral pain associated with colic in the horse.

Cattle: Flunixin Meglumine Injection is indicated for the control of pyrexia associated with bovine respiratory disease and endotoxemia. Flunixin Meglumine Injection is also indicated for the control of inflammation in endotoxemia.

Read accompanying directions carefully.

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

ot No. _____
rp. Date _____

NDC 59130-643-01
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FLUNIXIN MEGGLUMINE
INJECTION 50 mg/mL

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ANADA 200-124, APPROVED BY FDA

AmTech
Group, Inc.

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Edetate Disodium 0.1 mg
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Propylene Glycol 207.2 mg
Phenol (as preservative) ... 5.0 mg
Water For Injection q.s.
with hydrochloric acid to adjust pH

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within four days of the last treatment. Not for use in lactating or dry dairy cows. A withdrawal period has not been established for this product in preparturient calves. Do not use in calves to be processed for veal. Not for use in horses intended for food.

Store between 2° and 30°C (36° and 86°F).

600052 Rev. 11-00

3 9130 64301 5

SB 12-26-00
ut 12-26-00
12-26-00 re 12/26/00 2001-2-01

CUSTOMER PROOF • CHECK CAREFULLY!

Customer: Phoenix Scientific P.O. #: Stephanie

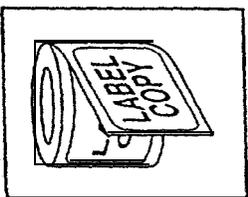
CYREL #: 14060 (sh) Date Sent: 5/25/00 11/29/00 12/6/00 12/18/00

LABEL: Flunixin Meglumine UNWIND #: 4

SIZE: 1.875" x 5"

VARNISH: YES PATTERN FLOOD
 NO

COLORS: 1797 red black water varn



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: _____

INDICATIONS: Horse: Flunixin Meglumine Injection is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also recommended for the alleviation of visceral pain associated with colic in the horse.

Cattle: Flunixin Meglumine Injection is indicated for the control of pyrexia associated with bovine respiratory disease and endotoxemia. Flunixin Meglumine Injection is also indicated for the control of inflammation in endotoxemia.

Read accompanying directions carefully.



600052 Rev. 11-00

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

NDC 59130-643-02

NET CONTENTS: 250 mL

**FLUNIXIN
MEGLUMINE**

INJECTION 50 mg/mL

For Intravenous or Intramuscular Use in Horses
and for Intravenous Use in Beef and Nonlactating
Dairy Cattle Only. Not for Use in lactating or
Dry Dairy Cows. Not for Use in Veal Calves.

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

**FOR ANIMAL USE ONLY
KEEP OUT OF REACH
OF CHILDREN**

ANADA 200.124. Approved by FDA



Each milliliter contains:
Flunixin Meglumine equivalent to
Flunixin 50 mg
Edetate Disodium 0.1 mg
Sodium Formaldehyde
Sulfoxylate 2.5 mg
Diethanolamine 4.0 mg
Propylene Glycol 207.2 mg
Phenol (as preservative) 5.0 mg
Water For Injection q.s.
with hydrochloric acid to adjust pH

RESIDUE WARNINGS: Cattle
must not be slaughtered for
human consumption within 4
days of the last treatment. Not for
use in lactating or dry dairy cows.
A withdrawal period has not
been established for this product
in preparturient calves. Do not
use in calves to be processed for
veal. Not for use in horses
intended for food.

Store between 2° and 30°C (36° and 86°F).

Lot No.

Exp. Date

INDICATIONS: Horse: Flunixin Meglumine injection is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also recommended for the alleviation of visceral pain associated with colic in the horse.

Cattle: Flunixin Meglumine injection is indicated for the control of pyrexia associated with bovine respiratory disease and endotoxemia. Flunixin Meglumine Injection is also indicated for the control of inflammation in endotoxemia.

Read accompanying directions carefully.



600052 Rev. 11-00

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

NDC 59130-643-02

NET CONTENTS: 250 mL

**FLUNIXIN
MEGLUMINE**

INJECTION 50 mg/mL

For Intravenous or Intramuscular Use in Horses
and for Intravenous Use in Beef and Nonlactating
Dairy Cattle Only. Not for Use in Lactating or
Dry Dairy Cows. Not for Use in Veal Calves.

CAUTION: Federal law restricts this drug to
use by or on the order of a licensed
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**FOR ANIMAL USE ONLY
KEEP OUT OF REACH
OF CHILDREN**

ANADA 200-124, Approved by FDA



Each milliliter contains:
Flunixin Meglumine equivalent to
Flunixin 50 mg
Edetate Disodium 0.1 mg
Sodium Formaldehyde
Sulfoxylate 2.5 mg
Diethanolamine 4.0 mg
Propylene Glycol 207.2 mg
Phenol (as preservative) 5.0 mg
Water For Injection q.s.
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A withdrawal period has not
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in preparturient calves. Do not
use in calves to be processed for
veal. Not for use in horses
intended for food.

Store between 2° and 30°C (36° and 86°F).

Lot No.

Exp. Date

CUSTOMER PROOF • CHECK CAREFULLY!

Customer: Phoenix Scientific P.O. #: Stephanie
CY REL #: 14061 (ts) Date Sent: 11/30/ 0 0 12/6/00 12/18/00

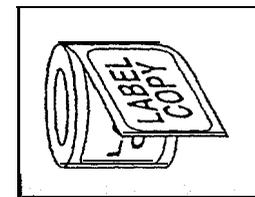
LABEL: Flunixin Meglumine

UNWIND #: 4

SIZE: 3 x 6

VARNISH: YES PA-TERN FLOOD
 NO

COLORS: 1797 red black water varn



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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: _____

12-26-00
12-26-00
12-26-00
12-26-00
1-2-01

AM/VT/BT

FLUNIXIN MEGGLUMINE INJECTION 50 mg/mL
For Intravenous Use in Horses and for
Intravenous Use in Beef and Nonlactating Dairy Cattle
Only. Not for Use in Lactating and Dry Dairy Cows.
Not for Use in Veal Calves

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

DESCRIPTION Each milliliter of Flunixin Meglumine Injection contains Runixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulfoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol; 5.0 mg phenol as preservative, hydrochloric add. water for injection q.s.

PHARMACOLOGY flunixin meglumine is a potent, non-narcotic, nonsteroidal, analgesic agent with anti-inflammatory and antipyretic activity. It is significantly more potent than pentazocine, meperidine and codeine as an analgesic in the rat; yeast paw test.

Horse: Flunixin is four times as potent on a mg-per-mg basis as phenylbutazone as measured by the reduction in lameness and swelling in the horse. Plasma half-life in horse serum is 1.6 hours following a single dose of 1.1 mg/kg. Measurable amounts are detectable in horse plasma at 8 hours post injection.

Cattle: Flunixin meglumine is a mat acid (pKa=5.82) which exhibits a high degree of plasma protein binding (approximately 99%). However, free (unbound) drug appears to readily partition into body tissues (V_d predictions range from 297 to 782 mL/kg.^{2,5} Total body water is approximately equal to 570 mL/kg).⁴ In cattle, elimination occurs primarily through biliary excretion.⁷ This may, at least in part, explain the presence of multiple peaks in the blood concentration-time profile following IV administration.²

In healthy cattle, total body clearance has been reported to range from 90 to 151 mL/kg/hr.^{2,5} These studies also report a large discrepancy between the volume of distribution at a steady state (V_d) and the volume of distribution associated with the terminal elimination phase (V_d). This discrepancy appears to be attributable to extended drug elimination from a deep compartment.⁶ The terminal half-life has been shown to vary from 3.14 to 8.12 hours.^{2,5}

Flunixin persists in inflammatory tissues⁹ and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations.^{4,9} These observations account for the counterclockwise hysteresis associated with flunixin's pharmacokinetic/pharmacodynamic relationships.¹⁰ Therefore, prediction of drug concentrations based upon the estimated plasma terminal elimination half-life will likely underestimate both the duration of drug action and the concentration of drug remaining at the site of activity.

INDICATIONS **Horse:** Flunixin Meglumine Injection is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also recommended for the alleviation of visceral pain associated with colic in the horse.

Cattle: Flunixin Meglumine Injection is indicated for the control of pyrexia associated with bovine respiratory disease and endotoxemia. Flunixin Meglumine Injection is also indicated for the control of inflammation in endotoxemia.

DOSE AND ADMINISTRATION **Horse:** The recommended dose for musculoskeletal disorders is 0.5 mg per pound (1 mL/100 lbs) of body weight once daily. Treatment may be given by intravenous or intramuscular injection and repeated for up to 5 days. Studies show onset of activity is within 2 hours. Peak response occurs between 12 and 16 hours and duration of activity is 24-36 hours.

The recommended dose for the alleviation of pain associated with equine colic is 0.5 mg per pound of body weight. Intravenous administration is recommended for prompt relief. Clinical studies show pain is alleviated in less than 15 minutes in many cases. Treatment may be repeated when signs of colic recur. During clinical studies approximately 10% of the horses required one or two additional treatments. The cause of colic should be determined and treated with concomitant therapy.

Cattle: The recommended dose for cattle is 1.1 to 2.2 mg/kg (0.5 to 1 mg/lb); 1 to 2 mL per 100 lbs) given by slow intravenous administration either once a day as a single dose or divided into two doses administered at 12-hour intervals for up to 3 days. The total daily dose should not exceed 2.1 mg/kg (1.0 mg/lb) of body weight. Avoid rapid intravenous administration of the drug.

CONTRAINDICATIONS **Horse:** There are no known contraindications to this drug when used as directed. Intra-arterial injection should be avoided. Horses inadvertently injected intra-arterially can show adverse reactions. Signs can be ataxia, incoordination, hyperventilation, hysteria, and muscle weakness. Signs are transient and disappear without antidotal medication within a few minutes. Do not use in horses showing hypersensitivity to flunixin meglumine.

Cattle: There are no known contraindications to this drug in cattle when used as directed. Do not use in animals showing hypersensitivity to flunixin meglumine. Use judiciously when renal impairment or gastric ulceration are suspected.

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 4 days of the last treatment. No: for use in lactating or dry dairy cows. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal. No: for use in horses intended for food.

PRECAUTIONS As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction.

Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of Flunixin Meglumine Injection with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.

Horse: The effect of Flunixin Meglumine Injection on pregnancy has not been determined. Studies to determine activity of Flunixin Meglumine Injection when administered concomitantly with other drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring adjunctive therapy.

Cattle: Do not use in bulls intended for breeding, as reproductive effects of Flunixin Meglumine Injection in these classes of cattle have not been investigated. NSAIDs are known to have potential effects on both parturition and the estrous cycle. There may be a delay in the onset of estrus if flunixin is administered during the prostaglandin phase of the estrous cycle. The effects of flunixin on imminent parturition have not been evaluated in a controlled study. NSAIDs are known to have the potential to delay parturition through a tocolytic effect. Do not exceed the recommended dose.

SAFETY **Horse:** A 3-fold intramuscular dose of 1.5 mg/lb of body weight: daily for 10 consecutive days was safe. No changes were observed in hematology, serum chemistry, or urinalysis values. Intravenous dosages of 0.5 mg/lb daily for 15 days; 1.5 mg/lb daily for 10 days; and 2.5 mg/lb for 5 days produced no changes in blood or urine parameters. No injection site irritation was observed following intramuscular injection of the 0.5 mg/lb recommended dose. Some irritation was observed following a 3-fold dose administered intramuscularly.

Cattle: No flunixin-related changes (adverse reactions) were noted in cattle administered a 1X (2.2 mg/kg; 1.0 mg/lb) dose for 3 days (three times the maximum clinical duration). Minimal toxicity manifested itself at moderately elevated doses (3X and 5X) when flunixin was administered daily for 9 days, with occasional findings of blood in the feces and/or urine. Discontinue use if hematuria or fecal blood are observed.

ADVERSE REACTIONS: In horses, isolated reports of local reactions following intramuscular injection, particularly in the neck, have been received. These include localized swelling, sweating, induration, and stiffness. In rare instances in horses, fatal or nonfatal clostridial infections or other infections have been reported in association with intramuscular use of Flunixin Meglumine Injectable. In horses and cattle, rare instances of anaphylactic-like reactions, some of which have been fatal, have been reported primarily following intravenous use.

HOW SUPPLIED Flunixin Meglumine Injection, 50 mg/mL, is available in 100 mL and 250 mL multidose vials.

STORE BETWEEN 2° AND 30° (36° AND 86°F).

REFERENCES:

- Johansson M, Anler EL. Gas chromatographic analysis of flunixin in equine urine after extractive methylation. *J Chromatogr.* 1988;427:55-66.
- Oldensvik K, Johansson M. High-performance liquid chromatography method for determination of flunixin in bovine plasma and pharmacokinetics after single and repeated doses of the drug. *Am J Vet Res.* 1995;56:489-495.
- Anderson KL, Neff-Davis CA, Davis LF, Bass VD. Pharmacokinetics of flunixin meglumine in lactating cattle after single and multiple intramuscular and intravenous administrations. *Am J Vet Res.* 1990;51:1464-1467.
- Oldensvik K. Pharmacokinetics of flunixin and its effect on prostaglandin F_{2α} metabolite concentration after oral and intravenous administration in heifers. *J Vet Pharmacol Ther.* 1995;18:254-259.
- Hardee GE, Smith JA, Harris SJ. Pharmacokinetics of flunixin meglumine in the cow. *Res Vet Sci.* 1985;39:110-112.
- Ruckebusch Y, Phaneuf LP, Dunlop R. Physiology of Small and Large Animals. Chapter 2: "Body fluid Compartments." Philadelphia, Pa: B.C. Decker; 1991:19.
- Kopcha M, Ahi AS. Experimental use of flunixin meglumine and phenylbutazone in food-producing animals. *J Am Vet Med Assoc.* 1989;194:45-49.
- Wagner JG. Significance of ratios of different volumes of distribution in pharmacokinetics. *Biopharm & Drug Dispos.* 1983;4:263-270.
- Lees P, Higgins AJ. Flunixin inhibits prostaglandin E₂ production in equine inflammation. *Res Vet Sci.* 1984;37:347-349.
- Landoni MF, Cunningham FM, Lees P. Determination of pharmacokinetics and pharmacodynamics of flunixin in calves by use of pharmacokinetic pharmacodynamic modeling. *Am J Vet Res.* 1995;56:786-794.

ANAO 200-124. Approved by FDA

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

60052

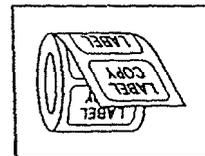
Rev. 11-00

CUSTOMER PROOF • CHECK CAREFULLY!

Customer: PHOENIX SCIENTIFIC P.O. #: STEPHANIE
YREL #: 14065 (TS) Date Sent: 12/7/00 12/22/00 1/9/01 01/23/01

LABEL: FLUNIXIN
SIZE: 3 x 7.5
VARNISH: YES]PAT-TERN FLOOD
E/NO
COLORS: BLK 1955 maroon

UNWIND #: 1



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Approved by: _____ Date approved: _____

581-26-01
871-29-01
11-29-01
1/10/01
= 33 1-30-01

RESIDUE WARNINGS: Caution must be observed for human consumption within 4 days of the last treatment. Not for use in lactating or dry dairy cows. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal. Not for use in horses intended for food.

Store between 2° and 30°C (36° and 86°F).

NDC 0051-0851-03

100 mL
Multiple-Dose Vial
50 mg/mL

Sterile

Banamine[®]

(FLUNIXIN MEGLUMINE)
Injectable Solution
Veterinary

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA #101-479, Approved by FDA.
Schering-Plough Animal Health

For intravenous or intramuscular use in horses and for intravenous use in beef and nonlactating dairy cattle only. Not for use in lactating or dry dairy cows. Not for use in veal calves.

Read accompanying directions carefully.
Copyright © 1985, 1993, Schering-Plough Animal Health Corp.
Kenilworth, NJ 07033. All rights reserved. 13259179 Rev. 6/97

LOT 0 CNX 104
EXP 5 02

F-13502676

PRODUCT
INFORMATION

NADA #101-479, Approved by FDA.

Banamine®
(FLUNIXIN MEGLUMINE)**Injectable Solution**
50 mg/mL

Veterinary

**For Intravenous or
Intramuscular Use in Horses
and for Intravenous Use in
Beef and Nonlactating Dairy
Cattle Only. Not for Use in
Lactating and Dry Dairy Cows.
Not for Use in Veal Calves.****CAUTION** Federal law restricts this drug to use by or on the order of a licensed veterinarian.**DESCRIPTION** Each milliliter of BANAMINE Injectable Solution contains flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulfoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol, 5.0 mg phenol as preservative, hydrochloric acid, wafer for injection q.s.**PHARMACOLOGY** Flunixin meglumine is a potent, non-narcotic, nonsteroidal, analgesic agent with anti-inflammatory and antipyretic activity. It is significantly more potent than pentazocine, meperidine, and codeine as an analgesic in the rat yeast paw test.**Horse:** Flunixin is four times as potent on a mg-per-mg basis as phenylbutazone as measured by the reduction in lameness and swelling in the horse. Plasma half-life in horse serum is 1.6 hours following a single dose of 1.1 mg/kg. Measurable amounts are detectable in horse plasma at 8 hours postinjection.**Cattle:** Flunixin meglumine is a weak acid (pKa=5.82) which exhibits a high degree of plasma protein binding (approximately 99%). However, free (unbound) drug appears to readily partition into body tissues (tissue predictions range from 217 to 782 mL/kg.¹³ Total body wafer is approximately equal to 570 mL/kg).¹⁴ In cattle, elimination occurs primarily through biliary excretion.¹⁵ This may, at least in part, explain the presence of multiple peaks in the blood concentration/time profile following IV administration.¹⁶In healthy cattle, total body clearance has been reported to range from 90 to 151 mL/kg/hr.¹⁷ These studies also report a large discrepancy between the volume of distribution at steady state (V_{ss}) and the volume of distribution associated with the terminal elimination phase (V_d). This discrepancy appears to be attributable to extended drug elimination from a deep compartment.¹⁸ The terminal half-life has been shown to vary from 3.14 to 8.12 hours.¹⁹Flunixin persists in inflammatory tissues²⁰ and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations.²¹ These observations account for the counterclockwise hysteresis associated with flunixin's pharmacokinetic/pharmacodynamic relationships.²² Therefore, predictions of drug concentrations based upon the estimated terminal elimination half-life will likely under-**INDICATIONS** **Horse:** BANAMINE Injectable Solution is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also recommended for the alleviation of visceral pain associated with colic in the horse.**Cattle:** BANAMINE Injectable Solution is indicated for the control of pyrexia associated with bovine respiratory disease and endotoxemia. BANAMINE Injectable Solution is also indicated for the control of inflammation in endotoxemia.**DOSE AND ADMINISTRATION** **Horse:** The recommended dose for musculoskeletal disorders is 0.5 mg per pound (1 mL/100 lbs) of body weight once daily. Treatment may be given by intravenous or intramuscular injection and repeated for up to 5 days. Studies show onset of activity is within 2 hours. Peak response occurs between 12 and 16 hours and duration of activity is 24.36 hours.

The recommended dose for the alleviation of pain associated with equine colic is 0.5 mg per pound of body weight. Intravenous administration is recommended for prompt relief. Clinical studies show pain is alleviated in less than 15 minutes in many cases. Treatment may be repeated when signs of colic recur. During clinical studies approximately 10% of the horses required one or two additional treatments. The cause of colic should be determined and treated with concomitant therapy.

Cattle: The recommended dose for cattle is 1.1 to 2.2 mg/kg (0.5 to 1 mg/lb; 1 to 2 mL per 100 lbs) given by slow intravenous administration either once a day as a single dose or divided into two doses administered at 12-hour intervals for up to 3 days. The total daily dose should not exceed 2.2 mg/kg (1.0 mg/lb) of body weight. Avoid rapid intravenous administration of the drug.**CONTRAINDICATIONS** **Horse:** There are no known contraindications to this drug when used as directed. Intra-arterial injection should be avoided. Horses inadvertently injected intra-arterially can show adverse reactions. Signs can be ataxia, incoordination, hyperventilation, hysteria, and muscle weakness. Signs are transient and disappear without antidotal medication within a few minutes. Do not use in horses showing hypersensitivity to flunixin meglumine.**Cattle:** There are no known contraindications to

mine. Use judiciously when renal impairment or gastric ulceration are suspected.

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Not for use in lactating or dry dairy cows. A withdrawal period has not been established for this product in preruminating calves. Do not use in calves to be processed for veal. Not for use in horses intended for food.**PRECAUTIONS** As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction.

Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of BANAMINE Injectable Solution with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.

Horse: The effect of BANAMINE Injectable Solution on pregnancy has not been determined. Studies to determine activity of BANAMINE Injectable Solution when administered concomitantly with other drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring adjunctive therapy.**Cattle:** Do not use in bulls intended for breeding, as reproductive effects of BANAMINE Injectable Solution in these classes of cattle have not been investigated. NSAIDs are known to have potential effects on both parturition and the estrous cycle. There may be a delay in the onset of estrus if flunixin is administered during the prostaglandin phase of the estrous cycle. The effects of flunixin on imminent parturition have not been evaluated in a controlled study. NSAIDs are known to have the potential to delay parturition through a tocolytic effect. Do not exceed the recommended dose.**SAFETY** **Horse:** A 3-fold intramuscular dose of 1.5 mg/lb of body weight daily for 10 consecutive days was safe. No changes were observed in hematology, serum chemistry, or urinalysis values. Intravenous dosages of 0.5 mg/lb daily for 15 days; 1.5 mg/lb daily for 10 days; and 2.5 mg/lb daily for 5 days produced no changes in blood or urine parameters. No injection site irritation was observed following intramuscular injection of the 0.5 mg/lb recommended dose. Some irritation was observed following a 3-fold dose administered intramuscularly.**Cattle:** No flunixin-related changes (adverse reactions) were noted in cattle administered a 1X (2.2 mg/kg; 1.0 mg/lb) dose for 9 days (three times the maximum clinical duration). Minimal toxicity manifested itself at moderately elevated doses (3X and 5X) when flunixin was administered daily for 9 days, with occasional findings of blood in the feces and/or urine. Discontinue use if hematuria or fecal blood are observed.**ADVERSE REACTIONS** In horses, isolated reports of

include localized swelling, sweating, induration, and stiffness. In rare instances in horses, fatal or nonfatal clostridial infections or other infections have been reported in association with intramuscular use of BANAMINE Injectable Solution. In horses and cattle, rare instances of anaphylactic-like reactions, some of which have been fatal, have been reported, primarily following intravenous use.

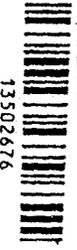
HOW SUPPLIED BANAMINE Injectable Solution, 50 mg/mL, is available in 50-mL (NDC 0061-0851-02), 100-mL (NDC 0061-0851-03), and 2% mL (NDC 0061-0851-04) multi-dose vials

Store between 2° and 30°C (36° and 86°F).

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