HFA-305

MAR 1 2006

Approval Date:_____

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-308

Flunixin Injection
(Flunixin meglumine)

This supplement allows for the use in lactating dairy cattle for control of pyrexia associated with bovine respiratory disease and endotoxemia and for the control of inflammation in endotoxemia.

Sponsored by:

Norbrook Laboratories, Ltd.

ANADA-200-308

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a. File Number	ANADA 200-308
b. Sponsor:	Norbrook Laboratories, Ltd. Station Works Newry BT35 6JP Northern Ireland Drug Labeler Code: 055529
c. Established Name:	Flunixin meglumine
d. Proprietary Name:	Flunixin Injectable
e. Dosage Form:	Injectable
f. How Supplied:	50 mL, 100 mL, and 250 mL multiple dose vials
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	Each milliliter contains flunixin meglumine equivalent to 50 mg flunixin
i. Route of Administration:	Horse: intramuscular or intravenous Cattle: intravenous
j. Species/Class:	Horse and cattle
k. Recommended Dosage:	Horse: 0.5 mg/pound (1 mL/100 lbs) of body weight once daily. Cattle: 1.1 to 2.2 mg/kg (0.5 to 1 mg/lb; 1 to 2 mL per 100 lbs) of body weight once a day as a single dose or divided into two doses administered at 12 hour intervals.
l. Pharmacological Category:	Non-narcotic, non-steroidal, analgesic, anti-inflammatory, and antipyretic.

m. 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.
n. Pioneer Product:	BANAMINE; flunixin meglumine; Schering-Plough Animal Health Corp.; NADA 101-479.
n. Effect of Supplement:	This supplement provides for the addition of use in lactating dairy cattle for the control of pyrexia associated with bovine respiratory disease and endotoxemia and for the control of inflammation in endotoxemia.

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, Phoenix Scientific, Inc. was granted a waiver from the requirement of an *in vivo* bioequivalence study for the generic product Flunixin Injection. The generic product is administered as an injectable, contains the same active ingredients 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, BANAMINE (flunixin meglumine) Injectable Solution, the subject of Schering-Plough Animal Health Corp. (NADA 101-479), was approved for use in horses on August 2, 1977 and approved for beef and non-lactating dairy cattle on May 6, 1998.

3. *HUMAN SAFETY:*

- **Tolerances for Residues:**

  The tolerance established for the pioneer product applies to the generic product. A tolerance 125 parts per billion (ppb) is established for flunixin free acid residues (the marker residue) in the liver (the target tissue), 25 ppb in the muscle, and 2 ppb in milk under 21 CFR 556.286. The acceptable daily intake (ADI) for total residues of flunixin meglumine is 0.72 micrograms per kilogram of body weight per day (21 CFR 556.286).

- **Withdrawal Times:**

  Because a waiver of the *in vivo* bioequivalence study was granted, the withdrawal times are those previously assigned to the pioneer product.

  The withdrawal time is four days in cattle and milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food.

- **Regulatory Method for Residues:**

  The procedure for the determination of flunixin residues in bovine liver is a high performance liquid chromatography (HPLC) method. The validated methods are on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

4. *AGENCY CONCLUSIONS:*

This supplemental ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that Flunixin Meglumine Injection, 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 200-308:
Flunixin Injection
50 mL multiple dose vial label
100 mL multiple dose vial label
250 mL multiple dose vial label
50 mL carton
100 mL carton
250 mL carton
Package Insert (Front)
Package Insert (Back)

Pioneer Labeling for NADA 101-479:
BANAMINE (flunixin Meglumine) Injectable Solution
50 mL multiple dose vial label
100 mL multiple dose vial label
250 mL multiple dose vial label
50 mL carton
100 mL carton
250 mL carton
Package Insert (Front)
Package Insert (Back)

RESIDUE WARNINGS:

Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

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

Flunixin Injection

FLUNIXIN MEGLUMINE

ANADA 200-3 [illegible] approved by FDA

[illegible] Solution

Veterinary

Not [illegible]

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

Norbrook

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

Read accompanying directions for use.

B.N.:

DOM:

EXP:

RESIDUE WARNINGS:

Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

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

Flunixin Injection

(FLUNIXIN MEGLUMINE)

ANADA 200-386, approved by FDA

Injectable Solution

Veterinary

Net Contents: 100ml

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

Norbrook

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

Read accompanying directions for use.

B.N.:

DOM:

EXP:

000020

RESIDUE WARNINGS:

Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

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

Flunixin Injection

(FLUNIXIN MEGLUMINE)

ANADA 200-308, approved by FDA

Injectable Solution

Veterinary

Net Contents: 250ml

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

Norbrook

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

Read accompanying directions for use.

B.N.:

DOM:

EXP:

Flunixin Injection
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary
ANADA 200-308, approved by FDA

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

50 mL

Norbrook

B.N.:
DOM:
EXP:
50 mL

Flunixin Injection
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary

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

Flunixin Injection
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary
ANADA 200-308, approved by FDA

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

50 mL

Norbrook

USA

Each mL contains: Flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulphoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol, 5.0 mg phenol as preservative, hydrochloric acid, water for injection q.s.

RESIDUE WARNINGS:
Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

Read accompanying directions carefully.

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

Flunixin Injection
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary
ANADA 200-308, approved by FDA

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

100 mL

Norbrook

B.N.:
DOM:
EXP:

100 mL

Flunixin Injection
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary

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

Flunixin Injection
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary
ANADA 200-308, approved by FDA

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

100 mL

Norbrook

USA

Each mL contains: Flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulphoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol, 5.0 mg phenol

as preservative, hydrochloric acid, water for injection q.s.

RESIDUE WARNINGS:
Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

Read accompanying directions carefully.

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

250 mL

B.N.:
DOM:
EXP:

Flunixin Injection
(FLUNIXIN MEGLUMINE)

Flunixin Injection
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary
ANADA 200-308, approved by FDA

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

250 mL

Norbrook

Flunixin Injection
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary

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

Flunixin Injection
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary
ANADA 200-308, approved by FDA

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

250 mL

Norbrook

USA

Each mL contains: Flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulphoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol, 5.0 mg phenol as preservative, hydrochloric acid, water for injection q.s.

RESIDUE WARNINGS:
Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

Read accompanying directions carefully.

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

FLUNIXIN INJECTION
(Flunixin Meglumine)

Injectable Solution 50 mg/mL
ANADA 200-308, approved by FDA

Veterinary

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

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

Description
Each milliliter of Flunixin Injection contains flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulphoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol, 5.0 mg phenol as preservative, hydrochloric acid, water for injection q.s.

Pharmacology
Flunixin meglumine is a potent, non-narcotic, non-steroidal, analgesic agent with anti-inflammatory and anti-pyretic 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 weak acid (pKa=5.82)[1] which exhibits a high degree of plasma protein binding (approximately 99%)[2]. However, free (unbound) drug appears to readily partition into body tissues (V_{SS} predictions range from 297 to 782 mL/kg.[2-5] Total body water is approximately equal to 570 mL/kg)[6]. 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 steady state (V_{SS}) and the volume of distribution associated with the terminal elimination phase (V_β). This discrepancy appears to be attributable to extended drug elimination from a deep compartment.[8] The terminal half-life has been shown to vary from 3.14 to 8.12 hours.[2-5]

Flunixin persists in inflammatory tissues[9] and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentration.[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 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 Injection is indicated for the control of pyrexia associated with bovine respiratory disease and endotoxemia. Flunixin 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 bodyweight once daily. Treatment may be given by intravenous or intramuscular injection and repeated for up to five 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 bodyweight. 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 the 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 1mg/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 bodyweight. Avoid rapid intravenous administration of the drug.

Contra-indications
Horse: There are no known contra-indications 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. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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 Flunixin Injection with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.
Horse: The effects of Flunixin Injection on pregnancy has not been determined. Studies to determine activity of Flunixin 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 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 1.5mg/lb of bodyweight daily for 10 consecutive days was safe. No changes were observed in hematology, serum chemistry, or urinalysis values. Intravenous dosages of 0.5mg/lb daily for 15 days; 1.5mg/lb daily for 10 days; and 2.5mg/lb daily for 5 days produced no changes in blood or urine parameters. No injection site irritation was observed following intramuscular injection of the 0.5mg/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 at 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 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 Injection. 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 Injection, 50 mg/mL, is available in 50 mL, 100 mL and 250 mL multi-dose vials.

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

REFERENCES

1. Johansson M, Anler EL. Gas chromatographic analysis of flunixin in equine urine after extractive methylation. *J Chromatogr.* 1988; 427:55-66
2. Odensvik 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.
3. Anderson KL, Neff-Davis CA, Davis LE, Base VD. Pharmacokinetics of flunixin meglumine in lactating cattle after single and multiple intramuscular and intravenous administrations. *Am J Vet Res.* 1990;51:1464-1467
4. Odensvik K. Pharmacokinetics of flunixin and its effect on prostaglandin $F_{2\alpha}$ metabolite concentrations after oral and intravenous administration in heifers. *J Vet Pharmacol Ther.* 1995;18:254-259.
5. Hardee GE, Smith JA, Harris SJ. Pharmacokinetics of flunixin meglumine in the cow. *Res Vet Sci.* 1985;39: 110-112
6. Ruckebusch Y, Phaneuf LP, Dunlop R. Physiology of Small and Large Animals. Chapter 2: "Body Fluid Compartments," Philadelphia, Pa: B.C. Decker, 1991:8-18
7. Kopcha M, Ahl AS. Experimental uses of flunixin meglumine and phenylbutazone in food-producing animals. *J Am Vet Med Assoc.* 1989;194:45-49
8. Wagner JG. Significance of ratios of different volumes of distribution in pharmacokinetics. *Biopharm & Drug Dispos.* 1983;4:263-270
9. Lees P, Higgins AJ. Flunixin inhibits prostaglandin E2 production in equine inflammation. *Res Vet Sci.* 1984;37: 347-349
10. 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.

Norbrook

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

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

NDC 0061-0851-02

50 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 dairy cattle.
Not for use in dry dairy cows and veal calves.
Read accompanying directions carefully.

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Schering-Plough Animal Health Corp.,
Union, NJ 07083.
All rights reserved.
Made in Germany.
27048005 Rev. 3/03
US 1033/1

Sample

USA051911LA

LOT
EXP

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

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

NDC 0061-0851-03

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 dairy cattle.
Not for use in dry dairy cows and veal calves.
Read accompanying directions carefully.

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Made in Germany.
24744710 Rev. 3/03

Sample

US 1029/1 USA051938LA

LOT
EXP

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

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

NDC 0061-0851-04

250 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 dairy cattle.
Not for use in dry dairy cows and veal calves.
Read accompanying directions carefully.

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Union, NJ 07083.
All rights reserved.
Made in Germany.
27048102 Rev. 3/03
US 1034/1

USA051946LA

LOT
EXP

Banamine®

(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary

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

Banamine®

(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary

LOT

EXP

US 4033/1

Each mL 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, water for injection qs.

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

Read accompanying directions carefully.
Store between 2° and 30°C (36° and 86°F).

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Schering-Plough Animal Health Corp.,
Union, NJ 07083.

All rights reserved. Made in Germany.
27075105 Rev. 3/03

DIE 4043

50 mL
Multiple-Dose Vial
50 mg/mL

Sterile

NDC 0061-0851-02

Banamine®

(FLUNIXIN MEGLUMINE)

Injectable Solution Veterinary

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

USA051989CA
FS010

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

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3 0061-0851-02 4

US 4033/1

DIE 4044

Banamine®
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary

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

USA051997CA
FS003

100 mL
Multiple-Dose Vial
50 mg/mL

Sterile

NDC 0061-0851-03

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

N
3 0061-0851-03 1

US 4029/1

Banamine®

(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary

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

sample

LOT

EXP

Banamine®
(FLUNIXIN MEGLUMINE)
Injectable Solution
Veterinary

Each mL 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, water for injection qs.

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

Read accompanying directions carefully.
Store between 2° and 30°C (36° and 86°F).

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27079202 Rev. 3/03

Banamine®

(FLUNIXIN MEGLUMINE)

Injectable Solution Veterinary

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

USA052004CA
FS025

250 mL
Multiple-Dose Vial
50 mg/mL

Sterile

NDC 0061-0851-04

Banamine®

(FLUNIXIN MEGLUMINE)

Injectable Solution Veterinary

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

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

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US 4034/2

Banamine®

(FLUNIXIN MEGLUMINE)

Injectable Solution Veterinary

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

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Banamine®
(FLUNIXIN MEGLUMINE)
Injectable Solution
Veterinary

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US 4034/2

Each mL 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, water for injection qs.

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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.

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26699010 Rev. 3/03

F-27050603

PRODUCT INFORMATION

USA051903INR
US 3029/1

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 Dairy Cattle. Not for Use in Dry Dairy Cows and Veal Calves.

sample

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, water for injection qs.

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)[1] which exhibits a high degree of plasma protein binding (approximately 99%).[2] However, free (unbound) drug appears to readily partition into body tissues (V_{SS} predictions range from 297 to 782 mL/kg.[2,4] Total body water is approximately equal to 570 mL/kg).[5] 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.[2,4] 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_β). This discrepancy appears to be attributable to extended drug elimination from a deep compartment.[8] The terminal half-life has been shown to vary from 3.14 to 8.12 hours.[2,4]

Flunixin persists in inflammatory tissues[9] 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:* 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, endotoxemia and acute bovine mastitis. 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 control of pyrexia associated with bovine respiratory disease and endotoxemia and control of inflammation in endotoxemia, is 1.1 to 2.2 mg/kg (0.5 to 1 mg/lb; 1 to 2 mL per 100 lbs) of body weight 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.

The recommended dose for acute bovine mastitis is 2.2 mg/kg (1mg/lb;2ml per 100lbs) of body weight given once by intravenous administration.

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. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in 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 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 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 250-mL (NDC 0061-0851-04) multi-dose vials.

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

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