

2008-200-124

APR 24 2008

Approval Date: \_\_\_\_\_

**FREEDOM OF INFORMATION SUMMARY**  
**SUPPLEMENTAL ABBREVIATED NEW ANIMAL**  
**DRUG APPLICATION**

**ANADA 200-124**

**Flunixin Meglumine Injection**  
**(flunixin meglumine)**

**Injectable Solution**

**Effect of the Supplement: to allow for the addition of a new  
indication for the control of pyrexia associated with acute bovine  
mastitis**

**Sponsored by:**

**IVX Animal Health, Inc.**

2008-200-124

F015

## FREEDOM OF INFORMATION SUMMARY

### 1. GENERAL INFORMATION:

- a. File Number: ANADA 200-124
- b. Sponsor: IVX Animal Health, Inc.  
3915 South 48th St. Terrace  
St. Joseph, MO 64503
- Drug Labeler Code 059130
- c. Established Name: Flunixin meglumine
- d. Proprietary Name: Flunixin Meglumine Injection
- e. Dosage Form: Injectable solution
- f. How Supplied: 100 and 250 mL multiple dose vials
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: Each mL contains flunixin meglumine equivalent to 50 mg of flunixin.
- i. Route of Administration: For intramuscular or intravenous use in horses and intravenous use in beef and dairy cattle
- j. Species/Class: Horses, not intended for human consumption; beef cattle; dairy cattle, lactating; dairy cattle, heifers not lactating; calves, excluding veal calves
- k. Recommended Dosage: Horses:  
0.5 mg/lb (1 mL/100 lbs) body weight once daily and repeated for up to 5 days.  
Cattle:  
1.1 to 2.2 mg/kg (0.5 to 1 mg/lb; 1 to 2 mL per 100 lbs) body weight given by slow intravenous administration either once a day as a single dose or divided into two doses 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. The dose for acute bovine mastitis is 2.2 mg/kg (1.0 mg/lb; 2 mL per 100 lbs).
- l. Pharmacological Category: Anti-inflammatory, anti-pyretic



(flunixin meglumine), the subject of Schering-Plough Animal Health Corp., NADA 140-479, was approved on August 2, 1977.

### **3. HUMAN SAFETY:**

The following are assigned to this product for cattle:

- **Tolerances for Residues:**

The tolerance established for the pioneer product applies to the generic product. A tolerance of 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:**

Under the CVM Bioequivalence Guidelines, when a generic product is granted a waiver of the in vivo bioequivalence testing, the withdrawal period established for the pioneer product is also assigned to the generic product.

For this reason, a withdrawal period of 4 days has been established for flunixin meglumine in cattle (21 CFR 522.970) 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 analytical method for the determination of flunixin meglumine 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 ANADA submitted under section 512(b)(2) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that 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 200-124

Flunixin Meglumine Injection- 100 mL and 250 mL container labels; package insert; and 100 mL and 250 mL case labels

Pioneer Labeling for NADA 101-479:

BANAMINE Injectable Solution- 50 mL, 100 mL, and 250 mL container labels, package insert, and 50 mL, 100 mL, and 250 mL carton labels

cc: Document Control Unit, for the administrative file of:  
A-200124-C-0045-OT  
Courtesy copy for the sponsor  
HFV-12, FOI Staff  
HFV-104, Green Book  
HFA-305, Division of Dockets Management

Other administrative information: APal/Generic Animal Drugs Team/April 9, 2008
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<p>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.</p>	<p>NOC 59130-824-01</p>	<p>Store between 2° and 30°C (36° and 86°F).</p>	<p>OPEN HERE ←</p>
<p><b>RESIDUE WARNINGS:</b> 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 pre-ruminating calves. Do not use in calves to be processed for veal. Not for use in horses intended for food.</p>	<p><b>Flunixin Meglumine Injection</b></p>	<p>Trademarks are property of IVX Animal Health, Inc.</p>	
<p>Read accompanying directions carefully.</p>	<p>80 mg/mL</p>	<p>Manufactured by IVX Animal Health, Inc. St. Joseph, MO 64503</p>	
<p>Lot No. Exp. Date</p>		<p>600052-01                      REV0208</p>	
		 <p>3 59130 82401 8</p>	

**PROJECT NAME: B055 Flunixin Meglumine Injection 100mL**  
**DATE: 03/17/08**  
**SCALE: 1"=1"**  
**SIZE: 1.875" X 5.75"**  
**COLORS: PMS 300, WARM GRAY 4, BLACK**

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.

**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.

Lot No.

Exp. Date

NDC 59130-824-02

# Flunixin Meglumine Injection

50 mg/mL

**IVX**

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

OPEN  
HERE  
←

Trademarks are property of  
IVX Animal Health, Inc.

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

600052-02

REV0208



PROJECT NAME: B056 Flunixin Meglumine Injection 250mL

DATE: 03/17/08

SCALE: 1"=1"

SIZE: 3" X6.75"

COLORS: PMS 300, WARM GRAY 4, BLACK

<p>ANADA 200,124, Approved by FDA</p> <p><b>Flunixin Meglumine Injection</b> 50 mg/mL</p> <p>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.</p> <p><b>CAUTION</b> Federal law restricts this drug to use by or on the order of a licensed veterinarian.</p> <p><b>DESCRIPTION</b> Each milliliter of Flunixin Meglumine Injection 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 q.s.</p> <p><b>PHARMACOLOGY</b> 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.</p> <p><b>Horse:</b> 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.</p> <p><b>Cattle:</b> Flunixin meglumine is a weak acid (pKa=5.82)<sup>1</sup> which exhibits a high degree of plasma protein binding (approximately 99%).<sup>2</sup> However, free (unbound) drug appears to readily partition into body tissues. <math>V_{d}</math> predictions range from 297 to 782 mL/kg.<sup>2,3</sup> Total body</p>	<p>water is approximately equal to 570 mL/kg.<sup>5</sup> In cattle, elimination occurs primarily through biliary excretion.<sup>7</sup> This may, at least in part, explain the presence of multiple peaks in the blood concentration/time profile following IV administration.<sup>2</sup></p> <p>In healthy cattle, total body clearance has been reported to range from 90 to 151 mL/kg/hr.<sup>2,8</sup> These studies also report a large discrepancy between the volume of distribution at a steady state (<math>V_{d,s}</math>) and the volume of distribution associated with the terminal elimination phase (<math>V_{d,t}</math>). This discrepancy appears to be attributable to extended drug elimination from a deep compartment.<sup>8</sup> The terminal half-life has been shown to vary from 3.14 to 8.12 hours.<sup>2,9</sup></p> <p>Flunixin persists in inflammatory tissues<sup>9</sup> and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations.<sup>4,9</sup> These observations account for the counterclockwise hysteresis associated with flunixin's pharmacokinetic/pharmacodynamic relationships.<sup>10</sup></p> <p>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.</p> <p><b>INDICATIONS</b> <b>Horse:</b> 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.</p> <p><b>Cattle:</b> Flunixin Meglumine Injection is indicated for the</p>	<p>control of pyrexia associated with bovine respiratory disease, endotoxemia and acute mastitis. Flunixin Meglumine Injection is also indicated for the control of inflammation in endotoxemia.</p> <p><b>DOSE AND ADMINISTRATION</b> <b>Horse:</b> The recommended dose for musculoskeletal disorders is 0.5 mg per pound (1 mL/100 lb) 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.</p> <p>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.</p> <p><b>Cattle:</b> 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 lb) 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.</p> <p>The recommended dose for acute bovine mastitis is 2.2</p>
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<p>mg/kg (1 mg/lb; 2 mL per 100 lb) of body weight given once by intravenous administration.</p> <p><b>CONTRAINDICATIONS</b> <b>Horse:</b> 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.</p> <p><b>Cattle:</b> 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.</p> <p><b>RESIDUE WARNINGS:</b> 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 pre-ruminating calves. Do not use in calves to be processed for veal. Not for use in horses intended for food.</p> <p><b>PRECAUTIONS</b> 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.</p>	<p>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.</p> <p><b>Horse:</b> 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.</p> <p><b>Cattle:</b> 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.</p> <p><b>SAFETY</b> <b>Horse:</b> 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</p>	<p>following a 3-fold dose administered intramuscularly.</p> <p><b>Cattle:</b> 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.</p> <p><b>ADVERSE REACTIONS</b> 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 injection. In horses and cattle, rare instances of anaphylactic-like reactions, some of which have been fatal, have been reported primarily following intravenous use.</p> <p><b>HOW SUPPLIED</b> Flunixin Meglumine Injection, 50 mg/mL, is available in 100 mL and 250 mL multidose vials.</p> <p>Store between 2° and 30°C (36° and 86°F).</p> <p><b>REFERENCES:</b></p> <ol style="list-style-type: none"> <li>Johansson M, Anter EL. Gas chromatographic analysis of flunixin in equine urine after extractive methylation. <i>J Chromatogr.</i> 1988;427:55-66.</li> <li>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. <i>Am J</i></li> </ol>
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<p>Vet Res. 1995;56:489-495.</p> <ol style="list-style-type: none"> <li>Anderson KL, Neff-Davis CA, Davis LE, Bass VD. Pharmacokinetics of flunixin meglumine in lactating cattle after single and multiple intramuscular and intravenous administrations. <i>Am J Vet Res.</i> 1990;51:1464-1467.</li> <li>Oldensvik K. Pharmacokinetics of flunixin and its effect on prostaglandin <math>F_{2\alpha}</math> metabolite concentrations after oral and intravenous administration in heifers. <i>J Vet Pharmacol Ther.</i> 1995;18:254-259.</li> <li>Hardee GE, Smith JA, Harris SJ. Pharmacokinetics of flunixin meglumine in the cow. <i>Res Vet Sci.</i> 1985;39:110-112.</li> <li>Ruckebusch Y, Phaneul LP, Dunlop R. Physiology of Small and Large Animals. Chapter 2: "Body Fluid Compartments." Philadelphia, Pa: B.C. Decker; 1991:8-18.</li> <li>Kopcha M, Ahi AS. Experimental uses of flunixin meglumine and phenylbutazone in food-producing animals. <i>J Am Vet Med Assoc.</i> 1989;194:45-49.</li> <li>Wagner JG. Significance of ratios of different volumes of distribution in pharmacokinetics. <i>Biopharm &amp; Drug Dispos.</i> 1983;4:263-270.</li> <li>Lees P, Higgins AJ. Flunixin inhibits prostaglandin <math>E_2</math> production in equine inflammation. <i>Res Vet Sci.</i> 1984;37:347-349.</li> <li>Landoni MF, Cunningham FM, Lees P. Determination of pharmacokinetics and pharmacodynamics of flunixin in calves by use of pharmacokinetic/pharmacodynamic modeling. <i>Am J Vet Res.</i> 1995;56:786-794.</li> </ol>	<p>Store between 2° and 30°C (36° and 86°F).</p> <p>Trademarks are property of IVX Animal Health, Inc.</p> <p>Manufactured by IVX Animal Health, Inc. St. Joseph, MO 64503</p> <p>600052-02 REV0208</p>  <p>3 59130 82402 5</p>
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PROJECT NAME: B056 Flunixin Meglumine Injection 250mL  
DATE: 03/17/08  
SCALE: 1"=1"  
SIZE: 3" X6.75"  
COLORS: PMS 300, WARM GRAY 4, BLACK

**FLUNIXIN MEGLUMINE  
INJECTION**

**50 mg/mL**

**12 x 100 mL**

LOT NO:                      EXP:

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

**IVX Animal Health**

St. Joseph, MO 64503



**FLUNIXIN MEGLUMINE  
INJECTION**

**50 mg/mL**

**12 x 100 mL**

LOT NO:                      EXP:

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

**IVX Animal Health**

St. Joseph, MO 64503



**FLUNIXIN MEGLUMINE  
INJECTION**

**50 mg/mL**

**12 x 100 mL**

LOT NO:                      EXP:

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

**IVX Animal Health**

St. Joseph, MO 64503



**FLUNIXIN MEGLUMINE  
INJECTION**

**50 mg/mL**

**12 x 250 mL**

LOT NO: EXP:

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

**IVX Animal Health**

St. Joseph, MO 64503



**FLUNIXIN MEGLUMINE  
INJECTION**

**50 mg/mL**

**12 x 250 mL**

LOT NO: EXP:

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

**IVX Animal Health**

St. Joseph, MO 64503



**FLUNIXIN MEGLUMINE  
INJECTION**

**50 mg/mL**

**12 x 250 mL**

LOT NO: EXP:

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

**IVX Animal Health**

St. Joseph, MO 64503



000018

**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 28 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 pre-milking calves. Do not use in calves to be processed for veal. Not for use in horses intended for food.

Store between 2° and 38°C (38° and 88°F).

NDC 0061-0851-02

50 mg/ml

Sterile

**Banamine®**  
(FLUNXIN MEGGLUMINE)  
Injectable Solution  
Veterinary

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

NADA #191-478, 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  
27048005 Rev. 3/03

US 1033/1

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LOT  
EXP

sample

**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 30 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 pregnant calves. Do not use in calves to be processed for veal. Not for use in horses intended for food.

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



NOC 0061-0651-03

100 ml  
50 mg/ml  
Sterile



**Banamine®**  
(FLUNXIN MEGLUMINE)  
Injectable Solution  
Veterinary

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.  
NADA # 991-478, 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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24241760 Rev. 2/03

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sample

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**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 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 0061-0851-04

250 mL  
Net Content (10.58 fl. oz.)  
50 mg/mL

Sterile

**Banamine®**  
(FLUNXIN MEGSUMINE)  
**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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27046102 Rev. 3/03

US 1034/1

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LUT  
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F-27050603

PRODUCT  
INFORMATION

USA0519031NR  
US 3029/1

NADA #101-478, 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 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 1.8 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 ( $pK_a=5.82$ )<sup>1</sup> which exhibits a high degree of plasma protein binding (approximately 99%).<sup>2</sup> However, free (unbound) drug appears to readily partition into body tissues ( $V_{ss}$  predictions range from 297 to 782 mL/kg.<sup>2,3</sup> Total body water is approximately equal to 570 mL/kg.<sup>4</sup> In cattle, elimination occurs primarily through biliary excretion.<sup>1</sup> This may, at least in part, explain the presence of multiple peaks in the blood concentration/time profile following IV administration.<sup>1</sup>

In healthy cattle, total body clearance has been reported to range from 90 to 151 mL/kg/hc.<sup>2,4</sup> 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.<sup>1</sup> The terminal half-life has been shown to vary from 3.14 to 8.12 hours.<sup>2,5</sup>

Flunixin persists in inflammatory tissues<sup>6</sup> and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations.<sup>4,9</sup> These observations account for the counterclockwise hysteresis associated with flunixin's pharmacokinetic/pharmacodynamic relationships.<sup>10</sup>

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 (1 mg/lb; 2 mL per 100 lbs) 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).

#### REFERENCES

1. Johansson M, Anier 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, 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.
4. Odensvik K. Pharmacokinetics of flunixin and its effect on prostaglandin F<sub>2α</sub> metabolite concentrations after oral and intravenous administration in heifers. *J Vet Pharmacol Ther.* 1995;18:254-259.
5. Hardea 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 E<sub>2</sub> 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.

March 2003

Schering-Plough Animal Health Corp.  
Kenilworth, NJ 07033

Made in Germany

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B-27050603

USA051903INV  
US 3029/1

**Banamine®**  
(FLUNIXIN MEGLUMINE)  
Injectable Solution  
Veterinary

DIE 2053

Each mL contains: flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edelate disodium, 2.5 mg sodium formaldehyde sulfonate, 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. Not for use in lactating or dry dairy cows. A withdrawal period has not been established for this product in premarketing calves. Do not use in calves to be processed for veal. Not for use in horses intended for food.

**Read accompanying directions carefully.**

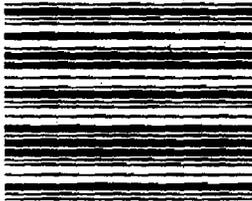
**Store between 2° and 30°C (36° and 86°F).**

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N 3 0061-0851-02 4

**Banamine®**  
(FLUNIXIN MEGLUMINE)  
Injectable Solution  
Veterinary



50 mL  
Multiple-Dose Vial  
50 mg/mL

Sterile

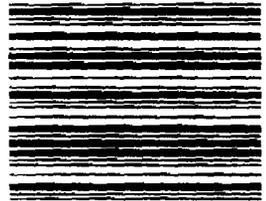
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**Banamine®**  
(FLUNIXIN MEGLUMINE)  
Injectable Solution  
Veterinary

**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



**Banamine®**  
(FLUNIXIN MEGLUMINE)  
Injectable Solution  
Veterinary

**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.**

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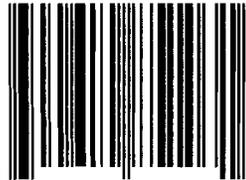
**Banamine®**  
 (FLUNIXIN MEGLUMINE)  
 Injectable Solution  
 Veterinary

**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 q.s.

**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.

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

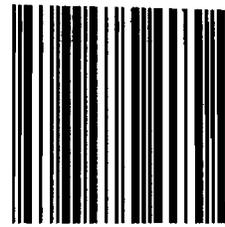
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N 3 0061-0851-03 1

**Banamine®**  
 (FLUNIXIN MEGLUMINE)  
 Injectable Solution  
 Veterinary

DIE 2054



100 mL  
 Multiple-Dose Vial  
 50 mg/mL

Sterile

NDC 0061-0851-03

**Banamine®**  
 (FLUNIXIN MEGLUMINE)  
 Injectable Solution  
 Veterinary

**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.**

**Banamine®**  
 (FLUNIXIN MEGLUMINE)  
 Injectable Solution  
 Veterinary

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

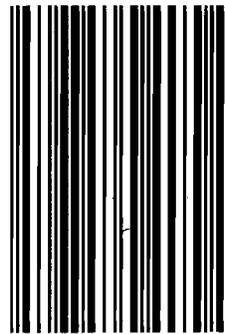
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Schering-Plough Animal Health

**Banamine®**  
 (FLUNIXIN MEGLUMINE)  
 Injectable Solution  
 Veterinary

**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.**



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**Banamine**<sup>®</sup>  
(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, 2.5 mg diethanolamine, 207.2 mg propylene glycol; 5.0 mg phenol as preservative, hydrochloric acid, water for injection q.s.

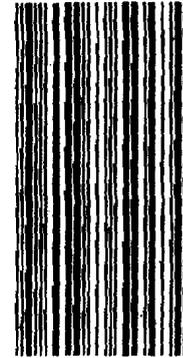
**RESIDUE WARNINGS:** Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Not for use in lactating or dry dairy cows. A withdrawal period has not been established for this product in preruminating calves. Do not use in calves to be processed for veal. Not for use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

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

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N 3 0061-0851-04 8



NDC 0061-0851-04

Sterile

250 mL  
Multiple-Dose Vial  
**50 mg/mL**

**Banamine**<sup>®</sup>  
(FLUNIXIN MEGLUMINE)  
Injectable Solution  
Veterinary

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

**Banamine**<sup>®</sup>  
(FLUNIXIN MEGLUMINE)  
Injectable Solution  
Veterinary

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

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NADA #101-479, Approved by FDA.

 Schering-Plough Animal Health

**Banamine**<sup>®</sup>  
(FLUNIXIN MEGLUMINE)  
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**For intravenous or intramuscular use in horses and for intravenous use in beef and non-lactating dairy cattle only. Not for use in lactating or dry dairy cows. Not for use in veal calves.**