

FLUNAZINE - flunixin meglumine injection, solution

Bimeda, Inc.

Flunazine®

(flunixin meglumine)

INJECTABLE SOLUTION

50 mg/mL *Sterile Solution*

Veterinary *Mutli-Dose Vial*

NOT FOR USE IN HUMANS

KEEP OUT OF REACH OF CHILDREN

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 Flunazine® Injectable Solution contains flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.2 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.

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 ($pK_a=5.82$)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_B). 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 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: Flunazine® 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: Flunazine® Injectable Solution is indicated for the control of pyrexia associated with bovine respiratory disease, endotoxemia and acute bovine mastitis. Flunazine® 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 is 1.1 to 2.2 mg/kg (0.5 to 1.0 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 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: NSAIDs inhibit production of prostaglandins which are important in signaling the initiation of parturition. The use of flunixin can delay parturition and prolong labor which may increase the risk of stillbirth. Do not use Flunazine® Injectable Solution within 48 hours of expected parturition. 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. Approved only for intravenous administration in cattle. Intramuscular administration has resulted in violative residues in the edible tissues of cattle sent to slaughter.

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

Flunazine® Injectable Solution with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.

Horse: The effect of Flunazine® Injectable Solution on pregnancy has not been determined. Studies to determine activity of Flunazine® 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 Flunazine® 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 flunixin meglumine. 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

Flunazine® Injectable Solution, 50 mg/mL, is available in 100 mL and 250 mL multi-dose vials.

STORE BETWEEN 2°C - 30°C (36°F - 86°F). PROTECT FROM FREEZING.

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, 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_{2a} 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;194:445-49.
8. Wagner JG. Significance of ratios of different volumes of distribution in pharmacokinetics. *Biopharm and 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.

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50 mg/mL Veterinary Sterile Solution Multi-Dose Vial

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ANADA# 200-387, Approved by FDA

Net Contents: 250 mL

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PROTECT FROM FREEZING.**

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

Read accompanying directions carefully.

Flunazine® is a Registered Trademark of Bimeda, Inc.

Manufactured by:
Bimeda-MTC Animal Health Inc.
Cambridge, ON Canada

Manufactured for:
Bimeda, Inc.
Le Sueur, MN 56058
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Product No. 1FLU004 8FLU007D Rev.05/12



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PULL

TAKEN
OBSERVE LABEL DIRECTIONS

FLUNAZINE

flunixin meglumine injection, solution

Product Information

Product Type	PRESCRIPTION ANIMAL DRUG	Item Code (Source)	NDC:6 1133-6006
Route of Administration	INTRAMUSCULAR, INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Flunixin Meglumine (UNII: 8Y3JK0JW3U) (Flunixin - UNII:356IB1O400)	Flunixin Meglumine	50 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61133-6006-2	100 mL in 1 VIAL, MULTI-DOSE		
2	NDC:61133-6006-3	250 mL in 1 VIAL, MULTI-DOSE		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANADA	ANADA200387	03/02/2006	

Labeler - Bimeda, Inc. (060492923)

Registrant - Bimeda, Inc. (060492923)

Establishment

Name	Address	ID/FEI	Business Operations
Bimeda-MTC Animal Health		256232216	manufacture

Revised: 11/2018

Bimeda, Inc.