HFA-305 Div of Doc Control

Date of Approval: NOV 1 2005

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 101-479

BANAMINE-S (flunixin meglumine) Injectable Solution

This supplement allows for use in swine for the control of pyrexia associated with swine respiratory disease.

Sponsored by:
Schering-Plough Animal Health Corp.

2005-101-479

FOIS 1

1. *GENERAL INFORMATION:*

a. File Number:	NADA 101-479
b. Sponsor:	Schering-Plough Animal Health Corp. 1095 Morris Ave. Union, NJ 07083 Drug Labeler Code: 000061
c. Established Name:	Flunixin meglumine
d. Proprietary Name:	BANAMINE-S (flunixin meglumine) Injectable Solution
e. Dosage Form:	Injectable solution
f. How Supplied:	100 mL multi-dose vials
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	50 mg flunixin free acid as the meglumine salt per mL
i. Route of Administration:	Intramuscular injection
j. Species/Class:	Swine
k. Recommended Dosage:	2.2 mg/kg (1 mg/lb; 2 mL per 100 lbs) of body weight given by a single intramuscular administration. The injection should be given only in the neck musculature with a maximum of 10 mL/site.
l. Pharmacological Category:	Non-steroidal anti-inflammatory drug (NSAID)
m. Indications:	For the control of pyrexia associated with swine respiratory disease.
n. Effect of Supplement:	This supplement allows for use in swine for the control of pyrexia associated with swine respiratory disease. This product has been approved for beef and lactating dairy cattle and horses.

2. *EFFECTIVENESS*

a. Dosage Characterization:

The current dose of flunixin approved in most EU countries for swine for the proposed indication is 2.2 mg flunixin/kg body weight (BW). Based on this, doses of 2.2 and 3.3 mg/kg were selected for further study in the US.

A model study was conducted to evaluate the effectiveness of flunixin administered IM once at 2.2 or 3.3 mg flunixin/kg BW as an adjunctive therapy to an antibiotic in comparison to a negative control treatment (antibiotic alone) in the treatment of acute pleuropneumonia in swine resulting from an *Actinobacillus pleuropneumoniae* (APP) seeder model infection.

Investigator: Kelly F. Lechtenberg, D.V.M., Ph.D.
Midwest Veterinary Services, Inc.
Oakland, NE

Design: After approximately 36 hours of being commingled with seeder pigs which had been challenged with APP, study candidate pigs that met inclusion criteria were allotted to three treatment groups (n=50/group) and treated once with an antibiotic plus a single injection of either flunixin at 2.2 or 3.3 mg flunixin/kg BW or normal saline. The pigs were observed clinically (rectal temperature, respiratory signs, adverse effects) until Day 5, when they were euthanized and necropsied.

Conclusion: Flunixin at 2.2 or 3.3 mg flunixin/kg BW significantly reduced rectal temperatures in treated pigs for the duration of the study. Both flunixin regimens reduced the percentage of pyretic pigs at 12 hours and on Days 1, 2, and 5. Because the 2.2 mg/kg and 3.3 mg/kg dosage regimens were clinically equivalent, the flunixin dose selected for further field studies was 2.2 mg flunixin/kg BW.

b. Substantial Evidence

Clinical Effectiveness & Field Safety (Study # C01-118-00)

1. Type of Study: Multi-site masked field trial in swine with spontaneously occurring swine respiratory disease.
2. Investigators:

   Site 01: Martin Mohr, D.V.M.
   Swine Veterinary Center
   St. Peter, MN

   Site 02: Kelly F. Lechtenberg, D.V.M., Ph.D.
   Midwest Veterinary Services, Inc.
   Oakland, NE

3. General Design

   a. Purpose: To evaluate the effectiveness and safety of BANAMINE-S (flunixin meglumine) Injectable Solution administered IM at 2.2 mg flunixin/kg BW, once, for the control of pyrexia in pigs associated with acute swine respiratory disease (SRD).

   b. Animals: Two hundred and thirty-two (232) crossbred swine ranging in age from 8 to 14 weeks with a body weight range of 10.8 to 74.7 kg were enrolled in this study. The pigs were randomly assigned to either a treated or control group.

   c. Controls: Sterile saline was administered IM.

   d. Inclusion Criteria: Animals from source herds that had a recent history of SRD were included in the study if they had pyrexia >104.5°F associated with dyspnea and depression. Evidence of SRD was confirmed pre-enrollment via necropsy and microbiological characterizations performed on 5 to 8 pigs from each potential batch of pigs that either met the inclusion criteria or were a recent mortality.

   e. Dosage Form: The commercial formulation of BANAMINE-S (flunixin meglumine) Injectable Solution containing 50 mg of flunixin free acid as the meglumine salt per mL.

   f. Route of Administration: IM injection in the neck

   g. Doses Used: Sterile saline was administered IM once at a volume equivalent to BANAMINE-S (flunixin meglumine) Injectable Solution administration. BANAMINE-S (flunixin meglumine) Injectable Solution was administered once at 2.2 mg flunixin/kg BW.

   h. Test Duration: 4 hours

   i. Pertinent Parameters Measured: The primary pivotal variable for this study was treatment success/failure rate for pyrexia. A pig was designated a treatment success if the rectal temperature decreased ≥ 2°F from the inclusion rectal temperature at 4 hours (± 30 minutes) after administration of the test article.

   j. A pig was designated a treatment failure if the rectal temperature did not decrease ≥ 2°F from the inclusion rectal temperature at 4 hours (± 30 minutes) after administration of the test article. If a pig died during the study, it was excluded retroactive to time 0 for the evaluation of treatment success/failure since this product is not an antibacterial agent, nor was it administered in conjunction with an antibacterial agent.

   k. Statistical analysis: For each site, the primary variable of treatment success/failure for pyrexia was analyzed using a generalized linear mixed model with binomial errors and a default logit link. The generalized linear mixed model included treatment (fixed effect), pen (random effect), and interaction of treatment by pen (random effect), and generated two-sided p-values.

      The secondary variable of rectal temperature was also analyzed with the general linear mixed model with treatment (fixed effect), pen (random effect), and

interaction of treatment by pen (random effect), and generated two-sided p-values.

4. Results

Statistically significantly higher success rates were seen after test article treatment. Each test site was analyzed separately. At site 01, the success rate in the BANAMINE-S (flunixin meglumine) Injectable Solution group was 33.9% as compared to 3.1% in the saline group. At site 02, the success rate in the BANAMINE-S (flunixin meglumine) Injectable Solution group was 21.0 % as compared to 6.3% in the saline group. At both sites, the BANAMINE-S (flunixin meglumine) Injectable Solution treatment group success rate was statistically significantly superior to the saline group ($p=0.0016$ and $p=0.0227$, respectively).

The analysis on mean rectal temperature at 4 hours resulted in a statistically significant difference between the two groups at both sites ($p<0.0001$ and $p=0.0004$, respectively).

5. Adverse Reactions

No drug related adverse events were observed during the conduct of this study. One pig in the control group died during the 4-hour post-test article administration phase. The pig was necropsied, and gross pathology confirmed pneumonia (suspect *Actinobacillus pleuropneumoniae*) as the cause of death.

6. Conclusions:

Under the conditions of this study, BANAMINE-S (flunixin meglumine) Injectable Solution was safe and effective for the control of pyrexia associated with acute swine respiratory disease at the target dose of 2.2 mg/kg BW injected IM in the neck.

3. *TARGET ANIMAL SAFETY*

A. Pivotal Study; Report 98531

1. Type of Study: Margin of Safety and Dose Tolerance (1X, 3X, 5X dose for 9X duration; and 10X dose for 3X duration)

2. Study Director: Terry N. TerHune, DVM, PhD
HMS Veterinary Development, Inc.
Tulare, CA

3. General Design:

   a. Purpose: To assess the safety of BANAMINE-S (flunixin meglumine) Injectable Solution to swine by IM injection at 1, 3, and 5 times the clinical dose of 2.2 mg of flunixin/kg body weight administered for 9 days (9X duration); and at 10 times the clinical dose administered for 3 days (3X duration).

   b. Animals: Sixty (30 castrated male and 30 female) healthy, growing, crossbred pigs approximately 3 months of age, weighing between 31 and 49 kg in body weight, were randomly assigned by sex to one of six treatment groups (n = 12/group).

   c. Control: 0.9% saline (USP)

   d. Test Article: BANAMINE-S (flunixin meglumine) Injectable Solution containing flunixin meglumine equivalent to 50 mg of flunixin/mL

   e. Route of Administration: IM injection in the neck area

   f. Doses: 2.2, 6.6, and 11.0 mg/kg body weight daily for 9 days; 22 mg/kg body weight daily for 3 days

   g. Test Duration: 10 days

   h. Pertinent Parameters/Observations: Clinical observations, physical examinations, feed and water consumption, body weights, hematology, serum chemistry, urinalysis, fecal examinations, gross pathology, and histopathology. Clinical pathology analyses were conducted on Days -16, -1, and approximately 24 hours after the third, sixth, and ninth doses.

   i. GLP Compliance Statement: The study was conducted in full compliance with FDA Good Laboratory Practice Regulations for Nonclinical Laboratory Studies (21 CFR Part 58).

   j. Statistical Analysis: Baseline values were used as a covariate for feed consumption, water consumption, and clinical pathology data. These data were analyzed using a repeated measures analysis of covariance. Histopathologic lesion incidence was analyzed using Fishers Exact Test with analysis by gender and dose levels. Clinical observations, urinalysis (except pH and specific gravity), and fecal analysis data were tabulated and summarized.

4. Results:

There were no treatment-related abnormal clinical observations or mortalities in the study. Daily feed and water consumption was similar among all groups. No treatment-related effects were observed in body weight, hematology, serum chemistry, urinalysis, and fecal examinations.

There were test article related increases in spleen weights in females in the 5X group. Spleen absolute and relative weights were statistically higher in the pigs administered 5X and 10X the proposed dose; however, no microscopic findings were correlated to increased spleen weights.

While there did appear to be a dose dependent increase in gastric ulcers in the treated groups, the control group had an incidence rate between the 5X and 10X groups.

Table 3.1: Incidence of Gastric Lesions

Group	Pars esophagea (cardia)	Fundus or Pylorus	Unspecified location	Total animals affected
Control	5	0	1	6
1X	1	1	1	3
3X	1	0	3	4
5X	3	1	0	4
10X	4 (1 multiple)	5 (1 multiple)	1 (1 multiple)	8
Total	**14**	**7**	**6**	**25**

There were treatment-related findings in the injection sites. Discolorations noted grossly correlated microscopically with muscle degeneration, fibrosis, and inflammation and/or hemorrhage. A dose-dependent increase in incidence and/or severity indicated that the test article was mildly irritating at the injection sites.

5. Conclusion:

The study demonstrated that BANAMINE-S (flunixin meglumine) Injectable Solution can be safely administered to growing swine at a single dose of 2.2 mg of flunixin/kg body weight.

B. Pivotal Study; Report 98530

1. Type of Study: Injection Site Irritation
2. Study Director: Terry N. TerHune, DVM, PhD
   HMS Veterinary Development Inc.
   Tulare, California

3. General Design of the Study:

   a. Purpose: To assess the resolution of injection site irritation, if any, of BANAMINE-S (flunixin meglumine) Injectable Solution when administered to swine by IM injection at a dose of 2.2 mg of flunixin/kg body weight administered for 3 days. A special emphasis of the pathologic evaluation was the identification of gross lesions which would require trim-out at the time of sacrifice if the animal was being processed for food for human consumption.

   b. Animals: Twenty (10 castrated male and 10 female) healthy, growing, crossbred pigs approximately 3 months of age and weighing between 34 and 49 kg were randomly assigned to 5 groups (n = 2 males and 2 females/group). Each group was sacrificed at a specified period after the last dose (4, 7, 14, 21, or 28 days, for groups 1, 2, 3, 4, and 5, respectively).

   c. Control: Not Applicable

   d. Test Article: BANAMINE-S (flunixin meglumine) Injectable Solution containing flunixin meglumine equivalent to 50 mg flunixin/mL.

   e. Route of Administration: Intramuscular injection in alternating sides of the neck for three consecutive days.

   f. Doses: All pigs received 2.2 mg flunixin/kg body weight

   g. Test Duration: 31 days

   h. Pertinent Parameters/Observations: Pigs were observed daily for clinical health status. Animals were euthanized 4, 7, 14, 21, or 28 days after the last dose. All injection sites and surrounding tissue were carefully dissected, grossly evaluated, photographed, and then collected. They were fixed in 10% neutral buffered formalin and evaluated histopathologically.

   i. GLP Compliance Statement: The study was conducted in full compliance with FDA Good Laboratory Practice Regulations for Nonclinical Laboratory Studies (21 CFR Part 58).

4. Results:

   There were no abnormal clinical observations during the course of the study. Animals treated with BANAMINE-S (flunixin meglumine) Injectable Solution showed signs of injection site irritation and damage that did not resolve in all animals by 28 days post-injection. Test article-related gross findings of red to tan discolorations at the injection site were limited to the deep musculature. One Group 4 animal had a fascial plane cyst at the injection site.

Table II. Incidence of gross lesions

Treatment Group* Gross Lesions	Group 1	Group 2	Group 3	Group 4	Group 5	Total (Sites)
Yes	1	4	10	10	8	33
No	11	8	2	2	4	27
Total (Sites)	12	12	12	12	12	60

*Group 1 = Treatments were given on Days 1-3 (necropsy 28 days post-dose)
*Group 2 = Treatments were given on Days 8-10 (necropsy 21 days post-dose)
*Group 3 = Treatments were given on Days 15-17 (necropsy 14 days post-dose)
*Group 4 = Treatments were given on Days 22-24 (necropsy 7 days post-dose)
*Group 5 = Treatments were given on Days 25-27 (necropsy 4 days post-dose)

5. Conclusion:

Lesions were typical of those commonly seen at IM injection sites and were not unexpected. There were signs of injection-site irritation and damage that did not resolve in all animals by 28 days post-injection, warranting an injection trim-out statement.

4. *HUMAN FOOD SAFETY*

a. Toxicology:

Toxicity studies with flunixin meglumine are described in the FOI Summary made available when NADA 101-479 was codified on July 20, 1998 (63 FR 38749).

b. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. SCH 14714 (Flunixin)-NMG: A Total Residue Depletion Study in Swine Following Intramuscular Administration of ^{14}C-SCH 14714-NMG, (SPRI Study No. 98131).

      1. Investigators:

Test Facility (In-Life):	Fred Thalacker, Ph.D. Principal Investigator Covance Laboratories, Inc. Madison, WI
Analytical Laboratories:	Fred Thalacker, Ph.D. Principal Investigator Covance Laboratories, Inc. Madison, WI
	Shailesh Vengurlekar, M.S., M.B.A. Principal Investigator ABC Laboratories Columbia, MO
	Mohammad Mushtaq, Ph.D. Study Director Schering-Plough Research Institute. Lafayette, NJ

      2. General Design of the Investigation:

         a. Purpose of the Study: The study was conducted to evaluate the tissue distribution, excretion and metabolism of ^{14}C-flunixin in swine following three intramuscular injections of ^{14}C-flunixin NMG 24 hours apart.

         b. Test system

            1. Animals: 22 mixed breed swine (11 barrows plus 11 gilts)

2. Weight: 33 to 47 kg (~70 days old)

3. Design:

Group #	Withdrawal (days)
I	1
II	4
III	7
IV	10
V	13
VI	Controls

c. Route of Drug Administration: Intramuscular in the cervical region of the neck

d. Time/Duration of Dosing: Three consecutive days

e. Radioisotope: The phenyl ring of flunixin was universally labeled with carbon-14.

f. Radiochemical purity: 99.9% (HPLC).

g. Results:

Mean concentrations of total radioactive residues (TRR), as flunixin free acid equivalents, are summarized in **Table 4.1**.

Table 4.1: Total radioactive residues as flunixin equivalents (ppm) in swine tissues

Day	1	4	7	10	13
Tissue	(mean ppm ± standard deviation; n=4)				
Liver	0.745±0.131	0.243±0.026	0.112±0.012	0.053±0.012	0.061±0.016
Kidney	0.552±0.168	0.115±0.013	0.042±0.003	0.025±0.003	0.023±0.006
Skin/Fat	0.028±0.004	0.012±0.004	0.008±0.002	0.005±0.000	0.005±0.001
Fat	0.027±0.009	0.007±0.002	0.003±0.001	0.002±0.002	0.001±0.001
Muscle	0.019±0.003	0.007±0.001	0.003±0.002	0.001±0.003	0.002±0.001
IS Muscle	10.2±15.8	0.128±0.033	0.068±0.074	0.147±0.183	0.006±0.004
IS Skin/Fat	5.39±9.45	0.054±0.022	0.145±0.236	0.080±0.133	0.026±0.031

Metabolism of ^{14}C-flunixin-NMG:

Flunixin was readily metabolized and eliminated with excretion of radioactivity essentially complete by 7 days post-final dose.

Non-injection site tissues from individual animals and injection site tissues pooled by sex from Groups II and/or I were extracted sequentially with hexane and ethyl acetate. If significant radioactivity remained, the unextractable residues in the post-extraction pellets (PEP) were then hydrolyzed in 6N HCl at 100 °C, and the hydrolysates were basified and extracted with ethyl acetate. The results are presented in **Table 4.2**.

The ethyl acetate extracts were analyzed separately by RP-HPLC for Groups II and/or I (4 and 1 days post-final dose, respectively). The residue components for the analyses of these extract fractions from each tissue were then summed to obtain the overall % TRR and the mean values are presented in **Table 4.3**.

Table 4.2: Extraction and acid hydrolysis of swine tissues

	Liver	Kidney	Skin/Fat	Fat	Muscle	IS Muscle	IS Skin/Fat
	Mean % TRR						
Day 1							
Hexane	1.6	1.2	36	35	5	28	21
ETOAc	25	29	83	28	38	85	47
PEP-ETOAc	45	40	ND	22	39	ND	6
PEP-Aqueous	16	39	ND	21	19	ND	3
Total	88	108	119	106	100	113	76
Day 4							
Hexane	<0.5	0.5	ND	ND	ND	45	30
ETOAc	6	6	ND	ND	ND	24	22
PEP-ETOAc	50	32	ND	ND	ND	ND	18
PEP-Aqueous	20	51	ND	ND	ND	ND	17
Total	76	90	ND	ND	ND	69	86

Table 4.3: Flunixin residues in swine tissues

	Tissue										
	Liver		Kidney		Skin/Fat	Fat	Muscle	IS Skin/Fat		IS Muscle	
Day	1	4	1	4	1	1	1	1	4	1	4
Residue											
Unk-1	0	0	0	0	0	1	0	0	0	0	0
4'-OH	0	0	0	0	5	11	3	0	0	0	0
Unk-1a	0	0	5	0	0	0	0	0	0	0	0
Unk-2	29	28	4	24	51	25	29	2	13	0	0
2'-OH-Me	0	1	4	4	5	17	8	0.4	2	0	0
5-OH	7	2	7	1	5	11	12	5	3	0	6
Unk-3	0	0	9	3	0	0	0	0	2	0	0
Flunixin	35	26	39	6	53	22	25	67	50	110	63
Unk-4	0	0	0	0	0	0	0	0	0	2	0
Remainder	16	20	39	51	0	21	19	3	17	0	0
Total	87	77	107	89	119	108	96	77	87	112	69

The HPLC chromatograms showed the presence in tissues of parent flunixin as well as the three identified flunixin metabolites:

4'-hydroxy flunixin
2'-hydroxymethyl flunixin
5-hydroxy flunixin

In addition, five unidentified flunixin metabolites were seen in the HPLC profiles of the tissue extracts. All of the unidentified metabolites except Unk-2 occurred only in small amounts and were not widely distributed in swine tissues. Because Unk-2 was a major metabolite and was widely distributed, further work was done to characterize that residue. Unk-2 was found to apparently consist of at least 10 components. The major component of Unk-2 was 30.5% of the total Unk-2 components with the remaining components between 2% and 18% of the total. Thus the major Unk-2 component in liver at Day 1 was approximately 8.8% of the TRR. Although the nature of the Unk-2 components remained unclear, it was determined that no further work was needed because the individual Unk-2 components would be expected to be at very low levels after withdrawal of the drug based on the observed rapid depletion of total residues in kidney and liver.

Tissues (except fat) from individual animals in all groups were analyzed by a determinative LC-MS/MS method for flunixin in swine tissues (SPRI SN 99036). The method included acid hydrolysis. The method limit of quantitation was 1 ppb for each tissue type. The mean ratios of flunixin to the TRR at all periods post-final dose are presented in **Table 4.4**.

Table 4.4: Ratio of flunixin by determinative method to TRR

Day	1	4	7	10	13
Tissue	(mean ratio flunixin:TRR)				
Liver	0.253	0.078	0.113	0.137	0.120
Kidney	0.331	0.053	0.061	0.085	0.126
Skin/Fat	0.273	0.103	0.122	BQL	BQL
Muscle	0.250	BQL	BQL	0.610	BQL
IS Skin/Fat	0.516	0.305	0.316	1.405	0.790
IS Muscle	0.979	0.447	0.390	0.081	0.199

b. Comparative metabolism in the rat and swine

Profiling of the major and minor ^{14}C-flunixin metabolites in swine was conducted utilizing the tissues generated in SCH 14714 (Flunixin)-NMG: A Total Residue Depletion Study in Swine Following Intramuscular Administration of ^{14}C-SCH 14714-NMG, (SPRI Study No. 98131).

A study of the metabolism and excretion of ^{14}C-flunixin meglumine in male and female Sprague-Dawley rats was conducted earlier for the approval of flunixin meglumine in beef cattle (NADA 101-479). In that work, rats were administered about 10 mg ^{14}C-flunixin meglumine/kg by gavage each day for seven consecutive days. The rats were sacrificed 2 hr after the final dose.

The findings are summarized in **Tables 4.5** and **4.6**.

The listings of flunixin metabolites in **Tables 4.5** and **4.6** show that unchanged flunixin and its three identified metabolites in swine tissue were also present in the tissues or excreta of the rat.

In addition to the identified flunixin metabolites, the analyses showed that there were five unidentified metabolites present in the tissues of swine. Because of differences in the chromatography used in the rat and swine studies, conclusive matching of the metabolites could not be done simply on the basis of HPLC retention time.

Although unknowns Unk-1, Unk-1a, Unk-3, and Unk-4 in the swine tissues were not conclusively matched with HPLC peaks in the rat metabolite profiles, they were judged not to be of human food safety concern because they were not widely found in swine tissues and were relatively minor in the amount present (<10% of the total residue each). Only traces of those metabolites are expected to occur in

tissues at and beyond the 12-day withdrawal time for the product, and there is no evidence to suggest that those metabolites would be of greater toxicological concern than for parent flunixin.

A comparison of the swine and rat metabolite profiles revealed that Unk-2 corresponded to a minor unknown residue observed in rat urine filtrates and feces extracts (Fr-6), which eluted between 4′-hydroxy flunixin and 2′-hydroxymethyl flunixin.

In summary, all metabolites of flunixin in swine tissues were either present in the rat or were of no greater toxicological concern than for parent flunixin due to low levels present or due to the fact that they were derived from bound residues of flunixin.

Table 4.5: Flunixin Residues in Rat Tissues and Excreta

	%TRR							
	Urine		Feces		Liver		Kidney	
	M	F	M	F	M	F	M	F
Residue	(RP-HPLC)				(2D-TLC)			
Fr-1	3.72	4.23	2.68	0.90	-	-	-	-
Fr-2	3.85	3.54	4.97	5.13	-	-	-	-
Fr-3	1.41	1.89	5.72	6.71	-	-	-	-
Fr-4	2.98	3.27	7.49	8.58	-	-	-	-
4'-OH	1.86	1.71	5.67	6.33	0	0	0	0
Fr-6	2.43	1.89	6.21	5.31	-	-	-	-
2'-OH-Me	10.20	10.08	9.58	6.06	0	0.59	0.38	0
Fr-8	7.97	7.95	6.90	8.21	-	-	-	-
Fr-9	3.45	4.14	4.53	7.28	-	-	-	-
5-OH	1.19	7.74	3.91	2.83	0.01	1.74	1.70	0
Flunixin	57.16	50.03	11.49	11.06	87.13	82.27	90.97	68.98
Fr-12	2.33	2.34	6.13	4.65	-	-	-	-
Fr-13	0.87	0.69	4.84	2.80	-	-	-	-
Fr-14	0.57	0.51	2.83	2.20	-	-	-	-
Methyl Ester	-	-	-	-	0.38	0.05	0.46	11.25
Other Extractable	0	0	0	4.03	7.58	6.82	5.33	19.25
Unextractable	0	0	17.05	17.92	4.90	8.54	1.17	0.52
Total	100	100	100	100	100	100	100	100

Table 4.6: Flunixin Residues in Swine Tissues

Tissue	Liver		Kidney		Skin/Fat	Fat	Muscle	IS Skin/Fat		IS Muscle	
Day	1	4	1	4	1	1	1	1	4	1	4
Residue											
Unk-1	0	0	0	0	0	1	0	0	0	0	0
4'-OH	0	0	0	0	5	11	3	0	0	0	0
Unk-1a	0	0	5	0	0	0	0	0	0	0	0
Unk-2	29	28	4	24	51	25	29	2	13	0	0
2'-OH-Me	0	1	4	4	5	17	8	0.4	2	0	0
5-OH	7	2	7	1	5	11	12	5	3	0	0
Unk-3	0	0	9	3	0	0	0	0	2	0	0
Flunixin	35	26	39	6	53	22	25	67	50	110	63
Unk-4	0	0	0	0	0	0	0	0	0	2	0
Remainder	16	20	39	51	0	21	19	3	17	0	0
Total	87	77	107	89	119	108	96	77	87	112	69

The listings of flunixin metabolites in **Tables 4.5** and **4.6** show that unchanged flunixin and its three identified metabolites in swine tissue were also present in the tissues or excreta of the rat.

In addition to the identified flunixin metabolites, the analyses showed that there were five unidentified metabolites present in the tissues of swine. Because of differences in the chromatography used in the rat and swine studies, conclusive matching of the metabolites could not be done simply on the basis of HPLC retention time.

Although unknowns Unk-1, Unk-1a, Unk-3, and Unk-4 in the swine tissues were not conclusively matched with HPLC peaks in the rat metabolite profiles, they were judged not to be of human food safety concern because they were not widely found in swine tissues and were relatively minor in the amount present (<10% of the total residue each). Only traces of those metabolites are expected to occur in tissues at and beyond the 12-day withdrawal time for the product, and there is no evidence to suggest that those metabolites would be of greater toxicological concern than for parent flunixin.

A comparison of the swine and rat metabolite profiles revealed that Unk-2 corresponded to a minor unknown residue observed in rat urine filtrates and feces extracts (Fr-6), which eluted between 4′-hydroxy flunixin and 2′-hydroxymethyl flunixin.

In summary, all metabolites of flunixin in swine tissues were either present in the rat or were of no greater toxicological concern than for parent flunixin due to low

levels present or due to the fact that they were derived from bound residues of flunixin.

c. SCH 14714 (Flunixin)-NMG: A Final Residue Depletion Study of SCH 14714-NMG in Swine (Fattening) Following IM Administration (SPRI Study No. 99227)

1. Investigators:

Test Facility (In-Life):	John W. Campbell, Ph.D. Principal Investigator Southwest Bio-Labs, Inc. Las Cruces, NM
Analytical Laboratory:	Bret Hurshman, B.S. Principal Investigator ABC Laboratories, Inc. Columbia, MO
	Mohammad Mushtaq, Ph.D. Study Director Schering-Plough Research Institute. Lafayette, NJ

2. General Design of the Investigation:

a. Purpose of the Study: The study was conducted to determine the concentration of marker residue, flunixin free acid, in swine tissues as a function of time following three intramuscular injections of flunixin NMG in BANAMINE Injectable Solution 24 hours apart.

b. Test system

1. Animals: 32 (16 barrows plus 16 gilts) large white mixed breed fattening swine

2. Weight: 53 to 71 kg (~18 weeks old)

3. Design:

Group #	Number of Animals	Withdrawal (days)
I	2M, 3F	1
II	3M, 2F	3
III	2M, 3F	5
IV	3M, 2F	7
V	2M, 3F	9
VI	3M, 2F	15
VII	1M, 1F	Controls

c. Test Article: Flunixin NMG (flunixin meglumine, BANAMINE); 50 mg (flunixin free acid)/mL as the commercial market-ready formulation

d. Route of Drug Administration: Intramuscular in the cervical region of the neck, alternating left and right sides

e. Dose: 2.2 mg flunixin free acid/kg body weight (nominal; actual dose 2.1-2.2 mg flunixin free acid/kg body weight)

f. Time/Duration of Dosing: Three consecutive days

g. Results: The mean flunixin levels for liver are summarized in **Table 4.7**.

Table 4.7: Summary of Flunixin Levels in the Liver of Swine Treated with 2.2 mg Flunixin (free acid)/kg/day IM for Three Days

Group	Withdrawal (Days)	Liver (mean±SD)
I	1	0.214±0.088
II	3	0.037±0.010
III	5	0.026±0.010
IV	7	0.014±0.006
V	9	0.014±0.005
VI	Should be 15	0.006±0.001

2. Target Tissue and Marker Residue Assignment

The SPRI Study No. 98131 with ^{14}C-flunixin in swine demonstrates that liver is the edible tissue of swine in which residues of flunixin are highest and persist the longest relative to their safe concentration. Therefore, liver is assigned as the target tissue for flunixin residues in swine. The metabolism data in that study showed that flunixin (as flunixin free acid) is the most abundant drug related residue in liver tissue. Therefore, flunixin (as the free acid) is assigned as the marker residue in swine.

3. Tolerance Assignments

The data provided in SPRI Study No. 98131, were used to determine the marker to total ratio for flunixin free acid (the marker residue) in swine liver (the target tissue). The marker to total residue data are summarized in **Table 4.8**.

Table 4.8: Total Residue Depletion Results: Total Residues and Flunixin (Determinative Assay [LC-MS/MS method]) in Liver

Day Post-Final Dose	Total Radioactive Residues (TRR) (ppm +/- Std. Dev.)	Mean Flunixin (Assay Results) (ppm)	Mean Ratio: Flunixin/TR
1	0.745 ± 0.131	0.172	0.23
4	0.243 ± 0.026	0.017	0.07
7	0.112 ± 0.012	0.011	0.10
10	0.053 ± 0.012	0.007	0.13
13	0.061 ± 0.016	0.006	0.10

The data show that the liver samples with the highest total residue values had a higher percentage of the marker residue (unchanged flunixin free acid) than did the samples with lower total residue values. However, there was not a consistent decline in the marker percentage as the total residue declined. At the time when total residues of ^{14}C-flunixin were near the safe concentration of 300 ppb, flunixin free acid (the marker residue) represented a mean percentage of 10% of the total radiolabeled residues. Therefore, a liver tolerance of 30 ppb (300 ppb X 0.1 = 30 ppb) is established for residues of flunixin free acid.

The muscle tolerance for flunixin free acid also was determined using data from SPRI Study No. 98131. In that study, there were only five muscle samples with measurable levels of unchanged flunixin. Four of those samples were from the one day withdrawal group, and the total residue levels in the four ranged from 16 ppb to 23 ppb. The levels of parent flunixin ranged from about 3 ppb to 6 ppb in those samples, which corresponded to a mean flunixin percentage of 24% of the total residue. This marker to total percentage was rounded to 25% and, with the muscle safe concentration of 100 ppb, was used to calculate the muscle tolerance of 25 ppb (100 ppb X 0.25 = 25 ppb).

4. Withdrawal Time

Using the data in study SPRI Study No. 99227 and our statistical tolerance limit algorithm for the 99th percentile, 95% confidence, a withdrawal period of 12 days is calculated for flunixin free acid administered intramuscularly at a nominal dose of 2.2 mg flunixin free acid.

c. Microbial Food Safety

An assessment of microbial food safety was not required for flunixin.

d. Regulatory Methods for Residues

1. Determinative Assay Procedure

The determinative assay for the marker residue, flunixin free acid, is a liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method which provides acceptable sensitivity, specificity, accuracy, and precision for the routine monitoring of flunixin free acid residues in swine liver.

Flunixin-NMG residues are converted to the marker residue, flunixin free acid, by acid-catalyzed hydrolysis. The pH of the hydrolysate is adjusted to 9.5-9.7 with NaOH and the aqueous layer is extracted with ethyl acetate. An aliquot is evaporated, reconstituted in sodium phosphate buffer, and applied to a pre-washed reverse phase, solid phase extraction column. The analyte is eluted from the column, under low vacuum, using methanol in water. The analyte is concentrated and the purified sample extract is transferred into an autosampler injection vial for LC-MS/MS analysis.

The method was demonstrated to reliably quantitate flunixin free acid residues at levels of 9 to 70 ppb. No interference was observed from 14 veterinary drugs commonly used in swine.

2. Confirmatory Assay Procedure

The confirmatory method also utilizes a liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) methodology applied to the purified solution obtained from the determinative method work-up. Dissociation of the parent ion $[MH]^+$ at m/z 297 yielded confirmatory ions at m/z 279 (base peak), 264, 259, and 239.

3. Display of the Method

The validated regulatory method for the determination and confirmation of residues of flunixin is on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

5. *AGENCY CONCLUSIONS*

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 514 of the implementing regulations. The data demonstrate that BANAMINE-S (flunixin meglumine) Injectable Solution when administered once at 2.2 mg flunixin/kg BW (1 mg/lb; 2 mL/100 lb) is safe and effective for the control of pyrexia associated with swine respiratory disease in swine.

A tolerance of 30 ppb for residues of flunixin free acid (marker residue) in liver (target tissue) of swine has been established. A withdrawal period of 12 days is required for this use of flunixin meglumine in swine. A tolerance of 25 ppb has also been established for residue of flunixin free acid in swine muscle.

Labeling restricts this drug to use by or on the order of a licensed veterinarian. This decision was based on the following factors: (a) the product contains a non-steroidal anti-inflammatory agent intended for therapeutic purposes and (b) adequate directions cannot be written to enable lay persons to appropriately decide in which animals this drug may be used safely.

Under Section 512(c)(2)(F)(iii) of the Federal Food, Drug and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The application contains investigations conducted or sponsored by the applicant that demonstrate animal safety and substantial evidence of effectiveness.

In accordance with 21 CFR 514.106(b)(2)(vii) this is a Category II change that did not require a reevaluation of the safety or effectiveness data in the parent application.

No patents were submitted with this application.

6. *ATTACHMENTS:*

Facsimile labeling is attached as indicated below:

A. Package insert

B. 100 mL bottle labeling

C. 100 mL carton labeling

F-28927207

PRODUCT INFORMATION

USA064398IN R
UB 3067

NADA #101-470, Approved by FDA.

Banamine®-S
(FLUNIXIN MEGLUMINE)

Injectable Solution
50 mg/mL
Veterinary

For intramuscular use in swine.
Not for use in breeding swine.

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

DESCRIPTION
Each milliliter of BANAMINE-S 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 q.s.

PHARMACOLOGY
Flunixin meglumine is a potent non-narcotic, non-steroidal, 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.

Flunixin is known to persist in inflammatory tissues[1] and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations[2]. Therefore, prediction of drug concentrations based upon 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.

The pharmacokinetic profiles were found to follow a 2-compartmental model, although a deep (third) compartment was observed in some animals. The mean terminal elimination half-life (β half-life) of flunixin after a single intramuscular injection of Banamine (2.2 mg/kg) to pigs was between 3 and 4 hours. The mean observed maximum plasma concentration was 2844 ng/mL, achieved at a mean time of approximately 0.4 hours. The mean $AUC_{(0-\infty)}$ was 6431 ng*hr/mL. Following IM administration of flunixin, quantifiable drug concentration could be measured up to 18 hours post dose. The mean volume of distribution was 2003 mL/kg and the mean total clearance was 390 mL/hr/kg. The mean absolute bioavailability of flunixin following an intramuscular injection in the neck was 87%.

INDICATION
BANAMINE-S Injectable Solution is indicated for the control of pyrexia associated with swine respiratory disease.

DOSE AND ADMINISTRATION
The recommended dose for swine is 2.2 mg/kg (1 mg/lb; 2 mL per 100 lbs) body weight given by a single intramuscular administration. The injection should be given only in the neck musculature with a maximum of 10 mL per site.

Note: Intramuscular injection may cause local tissue irritation and damage. In an injection-site irritation study, the tissue damage did not resolve in all animals by Day 28 post-injection. This may result in trim loss of edible tissue at slaughter.

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

RESIDUE WARNINGS
Swine must not be slaughtered for human consumption within 12 days of the last treatment.

PRECAUTIONS
As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Patients at greatest risk for adverse events are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed.

Since many NSAIDs possess the potential to produce gastrointestinal ulceration, concomitant use of flunixin meglumine with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided.

Not for use in breeding swine. The reproductive effects of BANAMINE-S Injectable Solution have not been investigated in this class of swine.

Intramuscular injection may cause local tissue irritation and damage. In an injection site irritation study, the tissue damage did not resolve in all animals by Day 28 post-injection. This may result in trim loss of edible tissue at slaughter.

SAFETY
Flunixin was mildly irritating at the injection sites. No other flunixin-related changes (adverse reactions) were noted in swine administered a 1X (2.2 mg/kg; 1.0 mg/lb) dose for 9 days. Minimal toxicity manifested itself as statistically significant increased spleen weight at elevated doses (5X or higher daily for 9 days) with no change in normal microscopic architecture.

HOW SUPPLIED
BANAMINE-S Injectable Solution, 50 mg/mL, is available in 100-mL (NDC 0000-0000-03), multi-dose vial.

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

REFERENCES

1. Lees P, Higgins AJ. Flunixin inhibits prostaglandin E_2 production in equine inflammation. *Res Vet Sci.* 1984; 37:347-349.
2. 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.

March 2005
Schering-Plough Animal Health Corp.
Union, NJ 07083

Made in Germany

Copyright© (2005)
Schering-Plough Animal Health Corp.
All rights reserved.

5-05

USA064401LA 28-07-2005 09:06 Pagina 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:
Swine must not be slaughtered for human consumption within 12 days of the last treatment.

Dosage and Administration:
For complete product information, please see the outer carton and package insert.

NDC 0000-0000-00
Sterile

[redacted]

Banamine®-S
(FLUNIXIN MEGLUMINE)
Injectable Solution
Veterinary

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA #101-470, Approved by FDA.

Schering-Plough Animal Health

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

For intramuscular use in swine.
Not for use in breeding swine.
Read accompanying directions carefully.

Copyright © (1985, 2003)
Schering-Plough Animal Health Corp.,
Union, NJ 07083.
All rights reserved.
Made in Germany 26927207 Rev. 1/06

LOT
EXP

US 1937 USA064401LA

USA064428CA 25-05-2005 14:14 Pagina 1

14 apr 05 • SPAH • BANAMINE-S • RIC #28927207 • PDR #40468 • PHARMACODE #687
'live' 4-4-2 100% barcode • 54,5 mm x 54,5 mm x 103,5 mm (100%) • OUTPUT @ 100% BY PM3

S/06477/48992

US 4687

Banamine®-S
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary

LOT

EXP

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:
Swine must not be slaughtered for human consumption within 12 days of the last treatment.

Dosage and Administration:
The recommended dose for swine is 2.2 mg/kg (1 mg/lb; 2 mL per 100 lbs) body weight given by a single intramuscular administration. The injection should be given in the neck.

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

Copyright © (1985, 2003)
Schering-Plough Animal Health Corp.,
Union, NJ 07083.
All rights reserved.
Made in Germany.

28927207 Rev. 1/06

DE 4044

Banamine®-S
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary

For intramuscular use in swine.
Not for use in breeding swine.

USA064428CA
FE003

NDC 0000-0000-00
Sterile

100 mL
Flunixin (as 50 mg/mL)
50 mg/mL

Banamine®-S
(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

FPO

N
3 1

US 4687

Banamine®-S
(FLUNIXIN MEGLUMINE)

Injectable Solution
Veterinary

For intramuscular use in swine.
Not for use in breeding swine.