ZUPREVO® (tildipirosin)

TECH BULLETIN

MERCK Animal Health

Efficacy of Zuprevo® (tildipirosin) or Draxxin® (tulathromycin) for Treatment of Naturally Occurring Bovine Respiratory Disease in Beef Calves

Key Highlights

- No differences existed in case fatality rates or treatment failures in beef calves diagnosed with naturally occurring BRD that were treated with Zuprevo or Draxxin.
- Zuprevo can be used as a successful treatment for BRD even after Micotil® (tilmicosin) has been used on arrival as a BRD control strategy.
- Rectal temperature of ≥ 104.5 °F at the time of allocation was associated with increased BRD case fatality risk.

ABSTRACT

Six hundred calves identified with BRD by feedyard pen riders were presented for further evaluation to a hospital facility. Calves that met the following criteria as determined by a veterinarian were randomly allocated to receive either Zuprevo® or Draxxin® to evaluate the clinical efficacy of these compounds for the treatment of naturally occurring BRD: a rectal temperature ≥ 104.0°F (≥ 40°C), no previous treatments for disease and no signs referable to disease of other organ systems. Eligible lots contained calves in two different risk categories: low or moderate risk of developing BRD that did not receive a metaphylactic antimicrobial at arrival and calves suspected to be at high risk of developing BRD that received a metaphylactic antimicrobial (tilmicosin) at feedlot arrival. After allocation, treated calves were returned to their home pen(s) and followed for 60 days. All enrolled animals that died during the study were gross necropsied by a veterinarian or trained feedlot personnel. There were no differences (P>0.12) in health outcomes between calves that received Zuprevo versus those that received Draxxin. Additionally, there were no differences in first treatment success or case fatality risk based on metaphylaxis status (P=0.54 and 0.95, respectively). Tildipirosin is an effective antimicrobial for first treatment of BRD in medium- to low-risk populations of cattle as compared with tulathromycin. This population represents the largest proportion of animals placed on feed in U.S. feedlots.[1]

INTRODUCTION

Zuprevo is an antimicrobial medication indicated for treatment and control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. When administered according to the label dose of 1 mL/100 lbs. of body weight (BW), tildipirosin is rapidly absorbed, distributes widely and provides concentrations in bovine lungs for an extended period.[2] This study was performed to compare the clinical efficacy of Zuprevo with Draxxin in the treatment of naturally occurring BRD. The conditions were typical of commercial feedlots and reflective of the majority of cattle placed in U.S. feedlots.

MATERIALS AND METHODS

This study was performed at a feedlot located in southwest Kansas, initiated November 3, 2017, and concluded May 15, 2018. Crossbred beef steers with an average enrollment body weight of 800 lbs. were used as test subjects.

Sample Size: Bovine respiratory disease case fatality risk was considered the primary outcome variable for this study. Baseline case fatality risk at this feedlot was historically at 7%. A sample size of 300 head per treatment group was estimated to detect a difference of 7 percentage points between groups with an alpha of 0.05 and beta of 0.20[a].

Animal Enrollment: Calves were observed daily by pen riders for identification of BRD based upon subjective evaluation including appearance, attitude, gauntness, nasal discharge and reluctance to move.[3] When calves presented these signs, they were pulled from home pens and moved to the hospital for confirmatory diagnosis. A veterinarian used the following criteria for study inclusion: in pen signs as reported by the pen riders, a rectal temperature of ≥ 104°F, no previous treatment for disease, lot cohorts with ≥ 60 days estimated to harvest, and absence of clinical signs referable to disease in other organ systems. Animals from eligible lots that did not receive an antibiotic at arrival processing were enrolled at any time. Animals from lots that did receive an arrival antibiotic, tilmicosin[b] (Micotil, Elanco Animal Health, Greenfield, IN; 13.2 mg/kg of body weight (BW) subcutaneously (SC); 2.0 mL/100 lbs. of BW) for control of BRD, were not eligible until ≥ 21 days post metaphylaxis.

Upon meeting the inclusion criteria, calves were randomly assigned to one of two treatment groups by lot of origin: either tildipirosin[c] (Zuprevo, Merck Animal Health, Whitehouse Station, NJ; 1 mL/100 lbs. of body weight subcutaneously in left neck) or tulathromycin[d] (Draxxin, Zoetis Animal Health, Parsippany, NJ; 1.1 mL/100 lbs. of body weight subcutaneously in left neck). Calves were enrolled in a 1:1 ratio within origin lot, identified with duplicate ear tags with both body weight and rectal temperature measured and recorded in a feedlot computer system[e]. Initial weight at enrollment was 801.2 (SE 10.15) with no difference (P=0.71) noted between those receiving Zuprevo and those receiving Draxxin as initial BRD treatment. Post-allocation, calves were evaluated for 60 days to monitor subsequent health outcomes.

BRD Retreatments: Calves were eligible for retreatment after a five-day post-treatment interval (PTI) was imposed for both Zuprevo and Draxxin. Pen riders, who were masked to experimental treatment, identified cattle that had met or exceeded the PTI, expressed signs of BRD morbidity and (or) had the appearance of lost body weight since first treatment as candidates in need of removal to a hospital for further evaluation. A rectal temperature ≥ 104 °F was used to confirm a BRD diagnosis. Calves requiring a second treatment for BRD were administered florfenicol[f] (Nuflor®, Merck Animal Health, Whitehouse Station, NJ; 6 mL/100 lbs. of body weight subcutaneously). A three-day PTI was used after the second treatment for BRD. Calves which required a third treatment for BRD were administered enrofloxacin[g] (Baytril®, Bayer Animal Health, Shawnee, KS; 4.5 mL/100 lbs. of body weight subcutaneously). There were no animals that required additional treatment.

Feed, Housing and Water: Calves were fed diets formulated to meet or exceed NASEM (2016) maintenance requirements and were equal across treatment groups.[4]

Statistical Analyses: Continuous outcomes (enrollment body weight and additional weights, enrollment rectal temperature and additional temperatures, and treatment death interval) were evaluated with linear mixed models. Binary outcomes (treatment successes and risk of case fatality) were evaluated using generalized logistic regression models. All models included a fixed effect for treatment group and random effects for lot of origin. Differences exhibiting a P value ≤ 0.05 were considered statistically significant. Additional models included fixed effect of treatment group; lots administered a metaphylactic antibiotic, treatment by metaphylaxis interaction and random effect for lot of origin[a]. Models evaluating body weight, rectal temperature and treatment success at third treatment would not converge when constructed as described; therefore, the random effect for origin lot was removed from these models.

RESULTS AND DISCUSSION

A total of 600 calves were enrolled into the study (Zuprevo = 299; Draxxin = 301) from an at-risk pool of 58,178 animals eligible during the enrollment phase. A total of seven removals occurred throughout the study. The cause for removal and numbers within the treatment group were as follows: two bloats and two heart failures in the Zuprevo treatment group and one calf died due to thromboembolic meningoencephalitis, one calf died due to atypical interstitial pneumonia and one calf with musculoskeletal injury during re-implant in the Draxxin treatment group. None of the removals were associated with treatments being evaluated based upon the investigator's

professional opinion. Removals occurred prior to analysis, which left 593 calves for final analysis (Zuprevo = 295; Draxxin = 298). Four hundred thirty were not administered a metaphylactic antibiotic upon arrival processing, whereas 163 calves were administered an antibiotic upon arrival processing and enrolled ≥ 21 days on feed.

There were no interactions (P>0.11) between treatment group and metaphylaxis status for health outcomes (data not shown). Rectal temperature at enrollment was 0.17°F greater (P=0.02) for no metaphylaxis cattle and 0.54°F greater (P=0.02) at third treatment for BRD for cattle that received metaphylaxis versus those that did not. The clinical significance of the rectal temperature at these times is unknown. It would seem highly unlikely that differences in rectal temperature at the time of first BRD pull, 21 days or greater after metaphylaxis, are the result of metaphylaxis administration. Differences in health outcome for cattle pulled for BRD and treated with Zuprevo or Draxxin were unremarkable (Table 1). First pull treatment success was 80.72% and 80.59% for cattle treated with Zuprevo or Draxxin, respectively (P=0.97). Third-pull treatment success was highly variable compared with first- and second-pull successes but not different (P=0.12) between BRD treatments. Case fatality risk percentage averaged 6.05% with no difference (P=0.89) between antibiotics used for first pull treatment. Rectal temperatures at the time of enrollment, second BRD treatment or third BRD treatment were not different (P>0.62) due to Zuprevo or Draxxin administration. Mean days to death after initial BRD treatment was different.

CONCLUSIONS

No health differences were identified in calves treated with Zuprevo compared to Draxxin for first treatment of BRD. Zuprevo is an effective antimicrobial for first treatment of BRD in the medium- to low-risk populations of cattle which represent the largest proportion of cattle on feed in the United States.[1] No differences in health outcomes were identified in the population that received a macrolide on arrival for control of BRD followed by a macrolide for treatment of BRD when the interval between metaphylaxis and first pull BRD treatment was ≥ 21 days on feed.

ZUPREVO IMPORTANT SAFETY INFORMATION: FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. TO AVOID ACCIDENTAL INJECTION, DO NOT USE IN AUTOMATICALLY POWERED SYRINGES WHICH HAVE NO ADDITIONAL PROTECTION SYSTEM. IN CASE OF HUMAN INJECTION, SEEK MEDICAL ADVICE IMMEDIATELY AND SHOW THE PACKAGE INSERT OR LABEL TO THE PHYSICIAN. DO NOT USE Zuprevo® 18% IN SWINE. Fatal adverse events have been reported following the use of tildipirosin in swine. NOT FOR USE IN CHICKENS OR TURKEYS. Cattle intended for human consumption must not be slaughtered within 21 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of this drug product in these cattle may cause milk residues. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal. The effects of Zuprevo® 18% on bovine reproductive performance, pregnancy and lactation have not been determined. Swelling and inflammation, which may be severe, may be seen at the injection site after administration. Subcutaneous injection may result in local tissue reactions which persist beyond slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.

NUFLOR IMPORTANT SAFETY INFORMATION: Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 38 days of subcutaneous treatment. Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal.

Table 1 Model-adjusted least square means (± SE) of health outcomes for first treatment of (BRD) by treatment group.

Outcome	Zuprevo	Draxxin	*P*-value*
Head enrolled	295	298	-
Treatment success[1], %			
First	80.72 (2.42)	80.59 (02.44)	0.97
Second	64.46 (7.30)	70.20 (07.49)	0.58
Third[1,2]	27.27 (13.43)	62.50 (17.12)	0.12
BRD case fatality risk, %	6.17 (1.95)	5.93 (1.95)	0.89
Rectal temperatures, ˚F			
Enrollment	104.71 (0.04)	104.68 (0.04)	0.62
Second Treatment	104.35 (0.07)	104.39 (0.08)	0.68
Third Treatment	104.35 (0.20)	104.48 (0.17)	0.62
Treatment death interval, days	21.98 (3.48)	14.46 (3.43)	0.13

[1] Treatment success defined as not requiring additional treatment for BRD and not dying within the 60-day monitoring period due to BRD.
[2] Third treatment outcomes did not include random effect for origin lot as no lots had multiple observations in calves treated three times.
*_P_-value displayed is main effect of treatment group. Model included random effect for origin lot.

Table 2 Model-adjusted least square means (± SE) of health outcomes for first treatment of BRD in calves stratified by rectal temperature.

Outcome	< 104.5˚F	≥ 104.5˚F	*P*-value*
Head enrolled	302	291	-
First treatment successes[1],%	84.52 (2.23)	76.71 (2.60)	0.02
BRD second treatment, %	11.59 (1.84)	17.18 (2.21)	0.05
BRD case fatality risk, %	4.29 (1.55)	7.87 (2.35)	0.05

[1] Treatment success defined as not requiring additional treatment for or dying from BRD within the 60-day monitoring period.
*_P_-value displayed is main effect of rectal temperature stratification; model included random effect for origin lot.

END NOTES

[a] R Studio Team 2016, Boston, MA
[b] Micotil®, Elanco Animal Health, Greenfield, IN
[c] Zuprevo®, Merck Animal Health, Whitehouse Station, NJ
[d] Draxxin®, Zoetis Animal Health, Parsippany, NJ
[e] Animal Management System, Animal Health International, Greeley, CO
[f] Nuflor®, Merck Animal Health, Whitehouse Station, NJ
[g] Baytril®, Bayer Animal Health, Shawnee, KS

REFERENCES

1. Menge M. et al. Pharmacokinetics of tildipirosin in bovine plasma, lung tissue, and bronchial fluid (from live, nonanesthetized cattle). *J Vet Pharmacol Ther.* 2012;35:550–559.

2. USDA Part IV: Health and health management on U.S. feedlots with a capacity of 1,000 or more head. 2011. Accessed July 3, 2018.

3. NASEM 2016: National Acadamies of Sciences, Engineering and Medicine. Nutrient Requirements fo Beef Cattle. Washington, DC: The National Academic Press.

4. Freedom of Information Summary NADA 141-334. (n.d.) Retrieved from http://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/3553

ZUPREVO™ 18%

(Tildipirosin)

Injectable Solution for Cattle

ANTIMICROBIAL DRUG:
180 mg of tildipirosin/mL

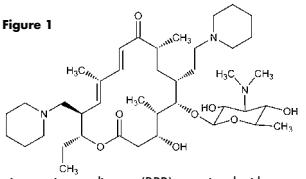
For subcutaneous injection in beef and non-lactating dairy cattle only. Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

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

DESCRIPTION: Zuprevo™ 18% is a ready-to-use sterile injectable solution containing tildipirosin, a semi-synthetic macrolide antibiotic. Each mL of Zuprevo18% contains 180 mg of tildipirosin as the free base, 82.5 mg citric acid monohydrate and 400 mg propylene glycol, and water qs with citric acid monohydrate added to adjust pH.

CHEMICAL NOMENCLATURE AND STRUCTURE:
Tildipirosin is the nonproprietary name for (11E,13E)-(4R,5S,6S,7R,9R,15R,16R)-6-(4-Dimethylamino-3,5-dihydroxy-6-methyl-tetrahydro-pyran-2-yloxy)-16-ethyl-4-hydroxy-5,9,13-trimethyl-7-(2-piperidin-1-yl-ethyl)-15-piperidin-1-ylmethyl-oxacyclohexadeca-11,13-diene-2,10-dione. The empirical formula is $C_{41}H_{71}N_3O_8$. The chemical structure of tildipirosin is shown below.

Figure 1



INDICATIONS: Zuprevo 18% is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni* in beef and and non-lactating dairy cattle, and for the control of respiratory disease in beef and non-lactating dairy cattle at high risk of developing BRD associated with *M. haemolytica, P. multocida,* and *H. somni.*

DOSAGE AND ADMINISTRATION: Inject subcutaneously as a single dose in the neck at a dosage of 4 mg/kg (1 mL/100 lb) body weight (BW). Do not inject more than 10 mL per injection site. Do not puncture the stopper of the respective vial size more than the tested number of punctures, shown in Table 1.

Clinical field studies indicate that administration of Zuprevo 18% (tildipirosin) Injectable Solution is effective for the control of respiratory disease in beef and non-lactating dairy cattle at "high risk" of developing BRD. Calves at high risk of developing BRD typically experience one or more of the following risk factors:

- Commingling from multiple sale barns/sources
- Extended transport times and shrink
- Exposure to wet or cold weather conditions or wide temperature swings
- Stressful arrival processing procedures (such as castration, dehorning, or branding)
- Recent weaning and poor vaccination history

Table 1 Number of punctures tested in the in-use study for the respective vial sizes

Vial size [mL]	Number of punctures tested in the in-use study
50	8
100	8
250	16

WARNINGS: FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. TO AVOID ACCIDENTAL INJECTION, DO NOT USE IN AUTOMATICALLY POWERED SYRINGES WHICH HAVE NO ADDITIONAL PROTECTION SYSTEM. IN CASE OF HUMAN INJECTION, SEEK MEDICAL ADVICE IMMEDIATELY AND SHOW THE PACKAGE INSERT OR LABEL TO THE PHYSICIAN.

Avoid direct contact with skin and eyes. If accidental eye exposure occurs, rinse eyes with clean water. If accidental skin exposure occurs, wash the skin immediately with soap and water. Tildipirosin may cause sensitization by skin contact.

For technical assistance or to report a suspected adverse reaction, call: 1-800-219-9286.
For customer service or to request a Material Safety Data Sheet (MSDS), call: 1-800-211-3573.
For additional Zuprevo 18% information go to www.zuprevo.com.
For a complete listing of adverse reactions for Zuprevo 18% reported to CVM see:
http://www.fda.gov/AnimalVeterinary/SafetyHealth.

DO NOT USE ZUPREVO 18% IN SWINE. Fatal adverse events have been reported following the use of tildipirosin in swine. NOT FOR USE IN CHICKENS OR TURKEYS.

RESIDUE WARNING: Cattle intended for human consumption must not be slaughtered within 21 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of this drug product in these cattle may cause milk residues. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS: The effects of Zuprevo 18% on bovine reproductive performance, pregnancy and lactation have not been determined. Swelling and inflammation, which may be severe, may be seen at the injection site after administration. Subcutaneous injection may result in local tissue reactions which persist beyond the slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.

CLINICAL PHARMACOLOGY: Similar to other macrolides, tildipirosin inhibits essential bacterial protein biosynthesis with selective binding to ribosomal subunits in a bacteriostatic and time-dependent manner. Tildipirosin may be bactericidal against certain isolates of *M. haemolytica* and *P. multocida.*

The following plasma pharmacokinetic (PK) properties of tildipirosin have been observed following a subcutaneous injection at a dose of 4 mg/kg BW in the neck:

Table 2 Summary of pharmacokinetic characterization of tildipirosin administered subcutaneously to calves at a dose of 4 mg/kg BW.

Parameter	Average	SD
C_{max} (ng/mL)	767*	284
T_{max} (hr)	0.75*	0.43
$AUC_{0\text{-last}}$ (hr·ng/mL)	21017**	3499
$AUC_{0\text{-inf}}$ (hr·ng/mL)	24934**	3508
$t_{1/2}$ (hr)	210**	53

* Value based on all 14 animals
** Value based on 8 animals that were slaughtered at 504 hr post-treatment.
C_{max}: maximum observed plasma concentration
T_{max}: Time at which Cmax was observed

$AUC_{0\text{-last}}$: Area under the plasma concentration versus time curve measured from time zero to the last sample with tildipirosin concentrations exceeding the limit of quantification of the analytical method

$AUC_{0\text{-inf}}$: AUC estimated from time zero to time infinity $t_{½}$: Terminal elimination half life

Due to the extensive partitioning of macrolides into tissues and because of their multi-fold greater concentrations in bronchial fluid relative to that observed in the blood, plasma drug concentrations underestimate concentrations at the site of action[1]. This is shown for tildipirosin in the following table, where bronchial fluid samples were collected in live, healthy calves, and compared to the concentrations in plasma observed in these same animals:

Table 3 Bronchial fluid-to-plasma ratio of tildipirosin in non-anesthetized cattle following a subcutaneous injection at a dose of 4 mg/kg BW in the neck

Time (hours)	Bronchial fluid (BF) concentration (ng/g)		Plasma (P) concentration (ng/mL)		BF/P Ratio
	Average	SD	Average	SD	
4	1543	895	297	81.8	5.20
10	2975	1279	242	96.7	12.3
24	3448	1433	136	53.9	25.4
72	3489	1712	70.7	29.0	49.3
96	1644	2024	60.2	29.0	27.3
120	1619	1629	52.3	19.9	30.9
240	1937	1416	27.1	10.8	71.5
336	1225	1682	26.1	9.2	47.0
504	935	1032	16.8	1.7	55.6

Tildipirosin concentrations in bronchial fluid collected *in vivo* from non-anesthetized cattle reflect the bacterial exposure to drug concentrations at the site of action.

[1]Nightingale, C.H. (1997) Pharmacokinetics and pharmacodynamics of newer macrolides. The Pediatric Infectious Disease Journal, 16, 438-443.

MICROBIOLOGY: Tildipirosin has shown *in vitro* and *in vivo* antibacterial activity against the bacteria *M. haemolytica, P. multocida,* and *H.somni,* three pathogens associated with BRD.

The minimum inhibitory concentrations (MICs) of tildipirosin against the indicated BRD pathogens were determined using the methods described in the M31-A2 standard of the Clinical and Laboratory Standards Institute (CLSI) and are shown in Table 4.

The MICs of tildipirosin were determined for isolates of *M. haemolytica, P. multocida,* and *H. somni* obtained from two BRD field studies. In both studies, tested isolates of *M. haemolytica* and *P. multocida* were obtained from nasopharyngeal swabs taken prior to treatment from all study animals. Tested isolates of *H. somni* were obtained from nasopharyngeal swabs taken prior to treatment from all study animals and from nasopharyngeal swabs taken from saline-treated animals classified as treatment failures.

Table 4 Tildipirosin minimum inhibitory concentration (MIC) values* of indicated pathogens isolated from BRD field studies in the U.S.

Indicated Pathogens	Year of isolation	Study	Number of isolates	MIC50** (µg/mL)	MIC90** (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	2007	Treatment	484	1	2	0.25 to >32
	2007 to 2008	Control	178	1	1	0.25 to >32
Pasteurella multocida	2007	Treatment	235	0.5	1	0.12 to >32
	2007 to 2008	Control	273	0.5	1	≤0.03 to 4
Histophilus somni	2007	Treatment	33	2	4	1 to 4
	2007 to 2008	Control	32	2	4	1 to >32

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

EFFECTIVENESS: In a multi-location field study, calves with naturally occurring BRD were treated with tildipirosin. The treatment success rate of the tildipirosin-treated group was compared to the treatment success rate in the saline-treated control group. A treatment success was defined as a calf not designated as a treatment failure from Day 1 to 13 and with normal attitude, normal respiration, and a rectal temperature of <104°F on Day 14. The treatment success rate was significantly higher (p=0.003) for the tildipirosin-treated group (229/300, 76%) compared to the saline-treated control group (96/200, 32%). There were no BRD-related deaths in the tildipirosin-treated group compared to a 7% (21/300) BRD-related mortality rate in the saline-treated group.

In another multi-location field study, calves at high risk for developing BRD were administered tildipirosin. The treatment success rate of the tildipirosin-treated group was compared to the treatment success rate in the saline-treated control group. A treatment success was defined as a calf not designated as a treatment failure based on clinical respiratory and attitude scoring and, if necessary, rectal temperature measurement of <104°F through the end of the study (Day 14). The treatment success rate was significantly higher (p=0.0001) for the tildipirosin-treated group (305/386, 79%) compared to the saline-treated group (197/387, 51%). There were three BRD-related deaths during the study (one tildipirosin-treated calf and two saline treated calves).

ANIMAL SAFETY: A target animal safety study was conducted using Zuprevo 18% administered in 5-month-old cattle as three subcutaneous doses of 4, 12, or 20 mg/kg BW given 7 days apart (1X, 3X, and 5X the labeled dose). Animals remained clinically healthy during the study at the labeled dose. Injection site swelling and inflammation, initially severe in some animals, was observed that persisted to the last day of observation (21 days after injection). No other drug-related lesions were observed macroscopically or microscopically at the labeled dose.

A separate injection site tolerance study was conducted using Zuprevo 18% in 5- to 9-month-old cattle administered as a single subcutaneous injection of 10 mL. Injection site swelling and inflammation, initially severe in some animals, was observed that persisted to the last day of observation (35 days after injection). No other drug-related clinical signs were observed.

STORAGE CONDITIONS: Do not store above 30°C (86°F). Do not freeze. The maximum storage time after first puncture is 28 days at or below 25°C (77°F).

HOW SUPPLIED: Zuprevo 18% is supplied in 50, 100 and 250 mL, amber glass, sterile, multi-dose vials.
U. S. Patent: 6,514,946
NADA 141-334, Approved by FDA
Use Only as Directed

Rev. 03/12
Made in Germany
Distributed by: Intervet Inc d/b/a Merck Animal Health, Summit, NJ 07901

MERCK Animal Health

NADA #141-063, Approved by FDA.

PRODUCT INFORMATION

180606 R1

Nuflor® (FLORFENICOL)

Injectable Solution 300 mg/mL

For intramuscular and subcutaneous use in beef and non-lactating dairy cattle only.

Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

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

DESCRIPTION NUFLOR Injectable Solution is a solution of the synthetic antibiotic florfenicol. Each milliliter of sterile NUFLOR Injectable Solution contains 300 mg of florfenicol, 250 mg N-Methyl-2-pyrrolidone, 150 mg propylene glycol, and polyethylene glycol qs. The chemical name for florfenicol is *2,2-Dichloro-N-[1-(fluoromethyl)-2-hydroxy-2-[4-(methylsulfonyl)phenyl]ethyl]acetamide.*

INDICATIONS NUFLOR Injectable Solution is indicated for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni*, and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.* Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni.*

DOSAGE AND ADMINISTRATION For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): NUFLOR Injectable Solution should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, NUFLOR Injectable Solution can be administered by a single subcutaneous (SC) injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

NOTE: Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

For control of respiratory disease in cattle at high-risk of developing BRD: NUFLOR Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

NUFLOR Injectable Solution DOSAGE GUIDE

ANIMAL WEIGHT (lbs)	IM NUFLOR DOSAGE 3.0 mL/100 lb Body Weight (mL)	SC NUFLOR DOSAGE 6.0 mL/100 lb Body Weight (mL)
100	3.0	6.0
200	6.0	12.0
300	9.0	18.0
400	12.0	24.0
500	15.0	30.0
600	18.0	36.0
700	21.0	42.0
800	24.0	48.0
900	27.0	54.0
1000	30.0	60.0

Recommended Injection Location

Do not inject more than 10 mL per injection site.

Clinical improvement should be evident in most treated subjects within 24 hours of initiation of treatment. If a positive response is not noted within 72 hours of initiation of treatment, the diagnosis should be re-evaluated.

CONTRAINDICATIONS Do not use in animals that have shown hypersensitivity to florfenicol.

WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. This product contains materials that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothing. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately. The Safety Data Sheet (SDS) contains more detailed occupational safety information.

For customer service, adverse effects reporting, and/or a copy of the SDS, cal 1-800-211-3573.

PRECAUTIONS: Not for use in animals intended for breeding purposes. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Toxicity studies in dogs, rats, and mice have associated the use of florfenicol with testicular degeneration and atrophy. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

RESIDUE WARNINGS: Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 38 days of subcutaneous treatment. This product is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

ADVERSE REACTIONS Inappetence, decreased water consumption, or diarrhea may occur transiently following treatment.

CLINICAL PHARMACOLOGY The pharmacokinetic disposition of NUFLOR Injectable Solution was evaluated in feeder calves following single intramuscular (IM) administration at the recommended dose of 20 mg/kg body weight. NUFLOR Injectable Solution was also administered intravenously (IV) to the same cattle in order to calculate the volume of distribution, clearance, and percent bioavailability1 (Table 1).

TABLE 1. Pharmacokinetic Parameter Values for Florfenicol Following IM Administration of 20 mg/kg Body Weight to Feeder Calves (n=10).

Parameter	Median	Range
C_{max} (µg/mL)	3.07*	1.43 - 5.60
T_{max} (hr)	3.33	0.75 - 8.00
T 1/2 (hr)	18.3**	8.30 - 44.0
AUC (µg•min/mL)	4242	3200 - 6250
Bioavailability (%)	78.5	59.3 - 106
Vd_{ss} (L/kg)***	0.77	0.68 - 0.85
Cl_t (mL/min/kg)***	3.75	3.17 - 4.31

* harmonic mean
** mean value
*** following IV administration

C_{max} Maxinum serum concentration
T_{max} Time at which C_{max} is observed
T 1/2 Biological half-life
AUC Area under the curve
Vd_{ss} Volume of distribution at steady state
Cl_t Total body clearance

Florfenicol was detectable in the serum of most animals through 60 hours after intramuscular administration with a mean concentration of 0.19 µg/mL. The protein binding of florfenicol was 12.7%, 13.2%, and 18.3% at serum concentrations of 0.5, 3.0, and 16.0 µg/mL, respectively.

MICROBIOLOGY Florfenicol is a synthetic, broad-spectrum antibiotic active against many Gram negative and Gram-positive bacteria isolated from domestic animals. It acts by binding to the 50S ribosomal subunit and inhibiting bacterial protein synthesis. Florfenicol is generally considered a bacteriostatic drug, but exhibits bactericidal activity against certain bacterial species. *In vitro* studies demonstrate that florfenicol is active against the bovine respiratory disease (BRD) pathogens *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni,* and that florfenicol exhibits bactericidal activity against strains of M. haemolytica and H. somni. Clinical studies confirm the efficacy of florfenicol against BRD as well as against commonly isolated bacterial pathogens in bovine interdigital phlegmon including *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.*

The minimum inhibitory concentrations (MICs) of florfenicol for BRD organisms were determined using isolates obtained from natural infections from 1990 to 1993. The MICs for interdigital phlegmon organisms were determined using isolates obtained from natural infections from 1973 to 1997 (Table 2).

TABLE 2. Florfenicol Minimum Inhibitory Concentration (MIC) Values* of Indicated Pathogens Isolated From Natural Infections of Cattle.

Indicated pathogens	Year of isolation	Isolate Numbers	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)
Mannheimia haemolytica	1990 to 1993	390	0.5	1
Pasteurella multocida	1990 to 1993	350	0.5	0.5
Histophilus somni	1990 to 1993	60	0.25	0.5
Fusobacterium necrophorum	1973 to 1997	31	0.25	0.25
Bacteroides melaninogenicus	1973 to 1997	20	0.25	0.25

* The correlation between the in vitro susceptibility data and clinical effectiveness is unknown.

** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

ANIMAL SAFETY A 10X safety study was conducted in feeder calves. Two intramuscular injections of 200 mg/kg were administered at a 48-hour interval. The calves were monitored for 14 days after the second dose. Marked anorexia, decreased water consumption, decreased body weight, and increased serum enzymes were observed following dose administration. These effects resolved by the end of the study.

A 1X, 3X, and 5X (20, 60, and 100 mg/kg) safety study was conducted in feeder calves for 3X the duration of treatment (6 injections at 48-hour intervals). Slight decrease in feed and water consumption was observed in the 1X dose group. Decreased feed and water consumption, body weight, urine pH, and increased serum enzymes, were observed in the 3X and 5X dose groups. Depression, soft stool consistency, and dehydration were also observed in some animals (most frequently at the 3X and 5X dose levels), primarily near the end of dosing.

A 43-day controlled study was conducted in healthy cattle to evaluate effects of NUFLOR Injectable Solution administered at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, NUFLOR Injectable Solution administration had no long-term effect on body weight, rate of gain, or feed consumption.

STORAGE INFORMATION Store between 2°-30°C (36°-86°F). Refrigeration is not required.

HOW SUPPLIED NUFLOR Injectable Solution is packaged in 100 mL (NDC 0061-1116-04), 250 mL (NDC 0061-1116-05), and 500 mL (NDC 0061-1116-06) glass sterile multiple-dose vials.

REFERENCE 1. Lobell RD, Varma KJ, et al. Pharmacokinetics of florfenicol following intravenous and intramuscular doses to cattle. J Vet Pharmacol Therap. 1994;17:253-258.

Made in Germany

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MERCK Animal Health