

WIN THE FIGHT
AGAINST BRD WITH

ZUPREVO[®]

(TILDIPIROSIN)



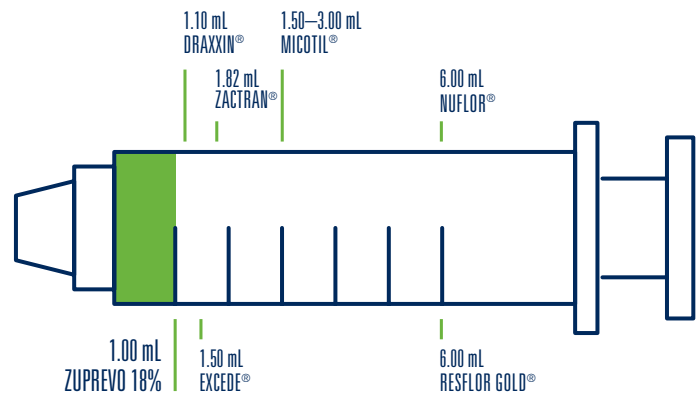
Take on the bacteria that cause BRD with the simple, single dose you want and the withdrawal time and results you need.



1 DOSE



APPROVED DOSAGE



PRE-SLAUGHTER WITHDRAWAL



SEE THE ZUPREVO DIFFERENCE

PRODUCT	ACTIVE INGREDIENT	INDICATIONS	APPROVED DOSAGE	LABEL TREATMENT	PRE-SLAUGHTER WITHDRAWAL
ZUPREVO 18%	<i>tildipirosin</i>	Treatment of BRD and control of respiratory disease	1 mL/100 lb.	1 dose	21 days
NUFLOR	<i>florfenicol</i>	Treatment of BRD and foot rot	6 mL/100 lb.	1 dose	28 days IM 38 days SC
RESFLOR GOLD	<i>florfenicol flunixin meglumine</i>	Treatment of BRD	6 mL/100 lb.	1 dose	38 days
BAYTRIL 100	<i>enrofloxacin</i>	Treatment and control of BRD	refer to label	refer to label	28 days
DRAXXIN	<i>tulathromycin</i>	Treatment and control of calf pneumonia, Treatment of pinkeye	1.1 mL/100 lb.	1 dose	18 days
EXCEDE	<i>ceftiofur crystalline free acid</i>	Treatment of BRD	1.5 mL/100 lb.	2 doses	13 days
MICOTIL	<i>tilmicosin</i>	Treatment of BRD	1.5 – 3 mL/100 lb.	1 dose	42 days
ZACTRAN	<i>gamithromycin</i>	Treatment of BRD	2 mL/110 lb.	1 dose	35 days

Resflor Gold (florfenicol and flunixin meglumine)

IMPORTANT SAFETY INFORMATION: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. This product contains material that can be irritating to skin and eyes. Animals intended for human consumption must not be slaughtered within 38 days of 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 preruminating calves. Do not use in calves to be processed for veal. Do not use in animals that have shown hypersensitivity to florfenicol or flunixin. Not for use in animals intended for breeding purposes. The effects of florfenicol and flunixin on bovine reproductive performance, pregnancy, and lactation have not been determined. When administered according to the label directions, RESFLOR GOLD may induce a transient local reaction in the subcutaneous and underlying muscle tissue.

Zuprevo 18% (tildipirosin)

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 (florfenicol) Injectable Solution:

IMPORTANT SAFETY INFORMATION: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. This product contains materials that can be irritating to skin and eyes. **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. 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. Not for use in animals intended for breeding purposes. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. 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.

BAYTRIL is a registered trademark of Bayer. DRAXXIN is a registered trademark of Zoetis. EXCEDE is a registered trademark of Zoetis. MICOTIL is a registered trademark of Elanco. ZACTRAN is a registered trademark of Merial.

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1/18 BV-ZUP-56948



PRODUCT INFORMATION
NADA 141-299, Approved by FDA.



(Florfenicol and Flunixin Meglumine)

Antimicrobial/Non-Steroidal Anti-Inflammatory Drug

For 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: RESFLOR GOLD® is an injectable solution of the synthetic antibiotic florfenicol and the non-steroidal anti-inflammatory drug (NSAID) flunixin. Each milliliter of sterile RESFLOR GOLD® contains 300 mg florfenicol, 16.5 mg flunixin as flunixin meglumine, 300 mg 2-pyrrolidone, 35 mg malic acid, and triacetin qs.

INDICATION: RESFLOR GOLD® is indicated for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*, and control of BRD-associated pyrexia in beef and non-lactating dairy cattle.

DOSAGE AND ADMINISTRATION: RESFLOR GOLD® should be administered once by subcutaneous injection at a dose rate of 40 mg florfenicol/kg body weight and 2.2 mg flunixin/kg body weight (6 mL/100 lb). Do not administer more than 10 mL at each site. The injection should be given only in the neck. Injection sites other than the neck have not been evaluated. For the 500 mL vial, do not puncture the stopper more than 20 times.

RESFLOR GOLD® Dosage Guide*	
ANIMAL WEIGHT (lbs)	DOSAGE (mL)
100	6.0
200	12.0
300	18.0
400	24.0
500	30.0
600	36.0
700	42.0
800	48.0
900	54.0
1000	60.0

Recommended Injection Location



* Do not administer more than 10 mL at each site.

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

WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. This product contains material 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 Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

For customer service or to obtain a copy of the MSDS, call 1-800-211-3573. For technical assistance or to report suspected adverse reactions, call 1-800-219-9286.

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 diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully

monitored. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that have not been previously diagnosed. Since many NSAIDs possess the potential to produce gastrointestinal ulceration, concomitant use of RESFLOR GOLD® with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored.

Flunixin is a cyclo-oxygenase inhibitory NSAID, and as with others in this class, adverse effects may occur with its use. The most frequently reported adverse effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported for other drugs in this class.

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. 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 toxic effect.

RESFLOR GOLD®, when administered as directed, may induce a transient reaction at the site of injection and underlying tissues that may result in trim loss of edible tissue at slaughter.

RESIDUE WARNINGS: Animals intended for human consumption must not be slaughtered within 38 days of 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: Transient inappetence, diarrhea, decreased water consumption, and injection site swelling have been associated with the use of florfenicol in cattle. In addition, anaphylaxis and collapse have been reported post-approval with the use of another formulation of florfenicol in cattle.

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
V _{dss} (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}: Maximum serum concentration
T_{max}: Time at which C_{max} is observed
T_{1/2}: Biological half-life
AUC: Area under the curve
V_{dss}: 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 *Bacteroides necrophorum* and *Bacteroides melaninogenicus*.

The minimum inhibitory concentrations (MICs) of florfenicol for BRD organisms were determined using isolates obtained from

PRODUCT INFORMATION

NADA #141-063, Approved by FDA.



Injectable Solution 300 mg/mL

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

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 Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

For customer service, adverse effects reporting, and/or a copy of the MSDS, call 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.



Injectable Solution for Cattle

ANTIMICROBIAL DRUG:
180 mg of tildipirosin/mL

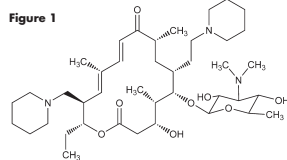
For subcutaneous injection in beef and non-lactating dairy cattle only. Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

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 Zuprevo 18% 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-yl-oxo)-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 C₄₁H₇₁N₅O₈. The chemical structure of tildipirosin is shown below.



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 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	* Value based on all 14 animals
T _{max} (hr)	0.75*	0.43	** Value based on 8 animals that were
AUC _{0-12hr} (hr·ng/mL)	21017**	3499	slaughtered at 504 hr post-treatment.
AUC _{0-inf} (hr·ng/mL)	24934**	3508	C _{max} : maximum observed plasma concentration
t _{1/2} (hr)	210**	53	T _{max} : Time at which C _{max} was observed

AUC_{0-inf}: 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-inf}: AUC estimated from time zero to time infinity t_{1/2}: 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 action¹. 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.

¹Nightingale, 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)
<i>Mannheimia haemolytica</i>	2007	Treatment	484	1	2	0.25 to >32
	2007 to 2008	Control	178	1	1	0.25 to >32
<i>Pasteurella multocida</i>	2007	Treatment	235	0.5	1	0.12 to >32
	2007 to 2008	Control	273	0.5	1	≤0.03 to 4
<i>Histophilus somni</i>	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

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