Comparison of the field efficacy of Zuprevo® (tildisporin), Nuflor® (florfenicol), Draxxin® (tulathromycin), and Bio-Mycin® 200 (oxytetracycline) as first-line therapies in cattle pulled for bovine respiratory disease.

SUMMARY

The first of its kind, this study was designed to evaluate the efficacy of Zuprevo® as a therapeutic treatment of Bovine Respiratory Disease (BRD) in a commercial feedlot setting when compared to three other antimicrobials commonly used in the industry.

Ultimately, the study determined:

- Zuprevo-treated steers and heifers had statistically ($p<0.01$) fewer first and second treatment relapses compared to those treated with Nuflor® and Bio-Mycin®.
- Zuprevo-treated steers and heifers had statistically similar ($p>0.05$) rates of railers and mortalities with intermediate costs between the other treatments.
- Zuprevo is an effective antibiotic when used to treat acute BRD in a population of yearling-type native cattle that did not receive mass antibiotic treatment upon arrival at the feedyard.

INTRODUCTION

Zuprevo (tildipirosin, 180 mg/ml) is in the macrolide class of antibiotics and is approved for the treatment and control of BRD. Approved for use in 2012, Zuprevo has been proven to be a useful antibiotic against respiratory disease in beef and dairy cattle production in both preventative and therapeutic roles. However, since its introduction, no field studies have been undertaken to assess the effectiveness of Zuprevo in a treatment role when compared to other widely used antimicrobials.

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MATERIALS AND METHODS

A total of 2,019 yearling steers and heifers pulled for respiratory disease were enrolled in the trial. Out of these initial enrollments, 1,516 met the criteria for inclusion.

Table 1

Breed:	Purebred or Cross Bred Beef Cattle
Source:	Mixed (auction, ranch-direct)
Sex:	Sex not limiting: Male castrate (MC) and /or Nonpregnant Female (F)
Weight Range:	250-454 kg (550-1000 lb.)
Age Range:	10-18 months
Physiological Status:	Cattle at moderate risk for development of BRD
Clinical Attitude Score (CAS)	CAS of 1,2,3 as defined below:
Clinical Attitude Score	Criteria
0	Normal; bright; alert; responsive
1	Mild depression; signs of weakness usually not present
2	Moderate depression; some signs of weakness; may be reluctant to stand
3	Severe depression; difficulty standing; head lowered or extended
4	Moribund

- Any animal that died within 48 hours of initial treatment was excluded. N=11
- Body temperature was recorded, but not used to determine BRD therapy
- No enrolled animals were given on-arrival antibiotics at the study site

TREATMENT ASSIGNMENT AND TREATMENTS

A pre-determined randomization schedule was used to assign treatments to cattle prior to treatment administration. The schedule was developed by randomly determining treatment order within the treatment block, which consisted of the four treatments (Zuprevo, Nuflor, Draxxin® or Bio-Mycin). As cattle were pulled for BRD and met the inclusion criteria previously described, they were administered treatment according to the randomization schedule. The second treatment was with Baytril® 10-0 5.7 cc/100#, the third treatment was with Advocin™ 2.0 cc/100#.

Table 2
Treatments and Post-Treatment Intervals

	Dose	Injection site	PTI	Number enrolled
Zuprevo	1.0 ml/cwt Sq	Neck	7 days	373
Draxxin	1.1 ml/cwt Sq	Neck	7 days	371
Bio-mycin	4.5 ml/cwt Sq	Neck	2 days	383
Nuflor	6.0 ml/cwt Sq	Neck	4 days	389

RESULTS

1,516 yearling cattle pulled for BRD were utilized to compare the effects of Zuprevo, Nuflor, Draxxin and Bio-Mycin on morbidity, mortality and railers when used as a first-line therapy in a commercial feedlot setting. Cattle were enrolled from November to April and did not differ at first time pull for rectal temperature, body weight, or clinical attitude score (P>0.20). As detailed in Table 3:

- Significantly fewer (p<0.01) Zuprevo-treated animals returned for a second treatment.
- Of the Zuprevo-treated animals returning for treatment, a significantly (p=0.017) smaller number of them required additional therapy.
- Zuprevo and Draxxin performed similarly with respect to subsequent therapy.

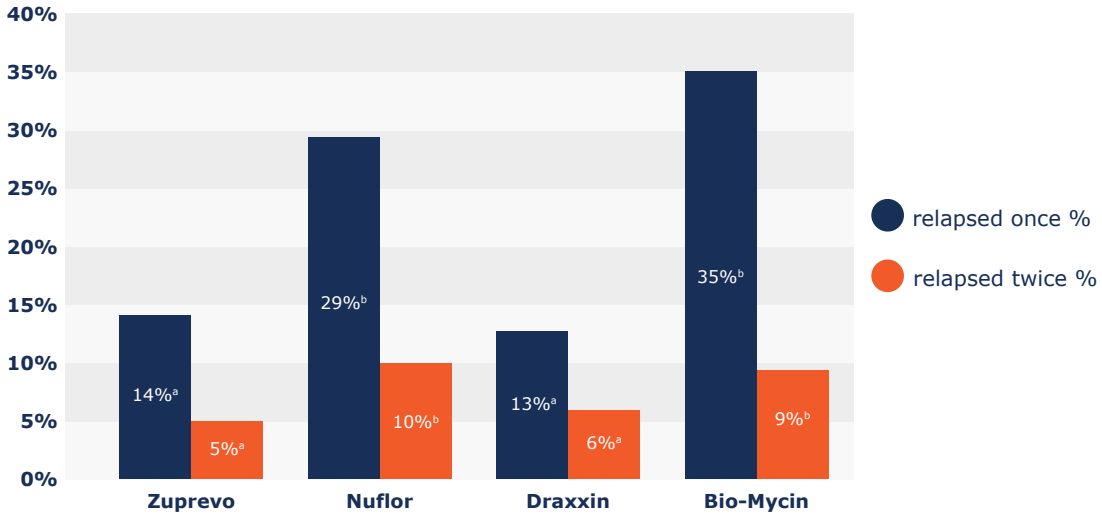
Table 3
Effects of BRD treatment on health parameters in moderate risk feedlot cattle.

Item[a]	Zuprevo	Nuflor	Draxxin	Bio-Mycin	P-Value	SEM
Number of treatments	373	371	383	389	—	—
1st respiratory relapse, %	14.2^{x}	28.6^{y}	12.8^{x}	35.2^{z}	< 0.01	2.4
2nd respiratory relapse, %	4.8^{x}	9.7^{y}	5.7^{x}	9.3^{y}	0.017	1.5
2nd treatment success rate[c], %	34.0^{yz}	34.0^{yz}	44.9^{y}	26.3^{z}	0.015	7.1
Respiratory mortality, %	2.15	2.70	2.35	3.09	0.856	0.88

[a] All items expressed as a percentage of head treated with the exception of "2nd respiratory relapse, %" denoted with superscript.
[c] Number of second respiratory relapses divided by number of first respiratory relapses.
^{xyz} Means in the same row that do not have a common superscript letter differ, P < 0.10.

Table 4 illustrates the differences between the products:

Table 4
Respiratory relapse percentage



[ab] Percentages for each category that do not have a common superscript letter differ, P < 0.10.

As found by Faber et al., 1999 and Cernicchiaro, et al., 2013, cattle requiring a second treatment for BRD were 30 to 50 percent less profitable at finish than those requiring only one treatment.[1,2]

ZUPREVO® (tildipirosin)

ZUPREVO® (tildipirosin)

FINANCIAL ANALYSIS

This study evaluated three premium antibiotics (Zuprevo, Nuflor, Draxxin) and a low-cost, long-acting tetracycline. The financial analysis (Table 5) shows the differences in health care costs associated with each therapy.

Table 5
Animal health costs for Zuprevo, Nuflor, Draxxin, and Bio-Mycin treatment groups.

Item[a]	Zuprevo	Nuflor	Draxxin	Bio-Mycin
Treatment costs[b]	$36.69	$36.91	$41.72	$12.87
First relapse costs[c]	$3.55	$7.52	$3.55	$9.25
Second relapse costs[d]	$1.77	$3.21	$1.77	$3.21
Total costs[e]	$42.01	$47.64	$47.04	$25.33

[a] All values expressed as a per-head treated basis.
[b] Therapy costs include a $9.50 chute charge to account for overhead plus $27.19, $27.41, $32.22, and $3.37 per head for Zuprevo, Nuflor, Draxxin, and Bio-Mycin, respectively. Antibiotic costs determined by using average treatment weight (768 lbs) multiplied by dose and cost/dose based off of current MWI Veterinary Supply prices as of October 30, 2015.
[c] Calculated as cost of first relapse treatment multiplied by the first relapse rate.
[d] Calculated as cost of second relapse treatment multiplied by the second relapse rate.
[e] Determined as the sum of treatment and relapse costs. Total costs are calculated as a per-head treated basis across treatments.
Total costs based on data showing no treatment difference in overall railers, mortality, or wastage.

- Zuprevo showed over a $5 advantage per head in health costs over the other premium antibiotics.
- Bio-Mycin was the lowest cost per head treated when only animal health costs were analyzed.

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CONCLUSION

In this study comparing Zuprevo, two other premium antibiotics (Nuflor and Draxxin) and a long-acting tetracycline (Bio-Mycin 200), Zuprevo proved effective and economical as a first-line therapy in treating yearling type cattle irrespective of temperature at first pull. The features of low dosage (1.0cc/cwt) and syringeability coupled with the benefits of decreased relapses and intermediate cost with statistically similar rates of railers and mortalities makes Zuprevo a valuable tool in the treatment of BRD in the feedyard.

References

1. R. Faber, N. Hartwig et.al, 1999. The costs and predictive factors of bovine respiratory diseases in standardized steer tests, Beef Research Report — Iowa State University, AS Leaflet R1648.
2. N. Cernicchiaro, B. White, D. Renter, A. Babcock. 2013. Evaluation of economic and performance outcomes associated with the number of treatments after an initial diagnosis of bovine respiratory disease in commercial feeder cattle. *AJVR*, Vol 74, No. 2, February 2013.

MERCK Animal Health

ZUPREVO®
(tildipirosin)

ZUPREVO® 18%

Intervet/Merck Animal Health
(Tildipirosin)
Injectable Solution for Cattle

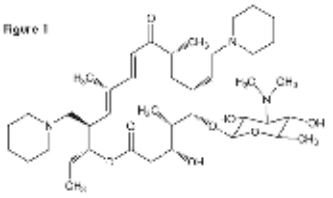
Antimicrobial Drug
180 mg of tildipirosin/mL
For subcutaneous injection in beef and non-lactating dairy cattle only.
Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

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 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-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 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 *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus 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 *Mannheimia haemolytica* and *Pasteurella multocida.*

The following plasma pharmacokinetic (PK) properties of tildipirosin have been observed following a subcutaneous injection at a dose of 4 mg/kg body weight 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 C_{max} was observed
$A_{UC0\text{-last}}$: 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
$A_{UC0\text{-inf}}$: 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 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 body weight in the neck

Time (hours)	Bronchial fluid (BF) concentration (ng/g)		Plasma (P) concentration (ng/mL)		BF/P Ratio
	Average	SD	Average	SD	
4	1043	895	297	81.8	5.20
16	2076	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	29.9	27.3
120	1019	1629	52.3	18.9	30.9
240	1937	1418	27.1	10.8	71.5
336	1225	1662	26.1	9.2	47.0
504	935	1332	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 *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni,* three pathogens associated with bovine respiratory disease (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 *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus 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 US.

Indicated Pathogens	Year of isolation	Study	Number of isolates	MIC50** (µg/mL)	MIC90** (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	2007	Treatment	464	1	2	0.25 to >32
	2007 to 2008	Control	176	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

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