ZUPREVO™ (tildipirosin) You're in control

# TECHNICAL BULLETIN

## Canadian commercial feedlot study[1] comparing Zuprevo™ to Draxxin® and Micotil® when used on arrival in calves at high risk of developing BRD

### SUMMARY

A commercial field study was conducted in Alberta to evaluate Zuprevo, Draxxin and Micotil when used for on-arrival treatment in high-risk calves. Health outcomes and feedlot performance to close-outs and carcass characteristics were compared.

There were no significant differences between calves treated with Zuprevo or Draxxin on all health and performance outcomes. Compared to Micotil-treated calves the Zuprevo group had a significantly lower first pull rate, lower overall mortality and a lower mortality due to histophilosis.

Also, Zuprevo-treated calves had significantly higher Yield Grade 1 carcasses and lower Yield Grade 2 carcasses than did Draxxin- or Micotil-treated calves.

Based on the results of this study, Zuprevo is more efficacious than Micotil and comparable to Draxxin, when administered as on-arrival therapy in feedlot calves at high risk of developing respiratory disease.

### OBJECTIVE

The study was conducted to evaluate the relative effect of Zuprevo on animal health, feedlot performance and carcass characteristic outcomes, when used as an on-arrival therapy in feedlot calves at high risk of developing BRD.

### MATERIALS AND METHODS

- Auction mart-sourced, exotic crossbred calves from western Canada were used in the study. Approximately 10,000 calves weighing 400-700 lb with predicted high risk of developing BRD were enrolled. Two study sites in Alberta were used (3 replicates per site). The animals were managed using the standard implant, vaccination, individual animal management, and pre-marketing feeding procedures determined by the investigators. The procedures used were standardized and applied to the three experimental groups at both sites.
- Each animal was uniquely identified with a CCIA RFID tag and a feedlot management tag, applied at processing. All identification tags were cross-referenced in the animal health software system. Feedlot processing included: vaccination against infectious bovine rhinotracheitis, bovine viral diarrhea, bovine respiratory syncytial virus, parainfluenza virus, *Histophilus somni, Mannheimia haemolytica* and clostridiosis, as well as administration of a pour-on endectocide.
- The calves were randomly allocated to one of the three experimental groups based upon the randomization table provided by the investigator. The animals assigned to each experimental group were housed in separate multi-pen lots, and sets of multi-pen lots were built sequentially until there were six replicates. Each replicate contained one multi-pen lot (508-620 head in two pens) for each experimental group.

[1]Data on file: S11414-00-MCR-CLI-RM, final report (November 26, 2012).



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- Treatment groups:

| | | |
|---|---|---|
| **Zuprevo** | 1 mL/100 lb (4 mg/kg) | 3,358 head |
| **Draxxin** | 1.1 mL/100 lb (2.5 mg/kg) | 3,359 head |
| **Micotil** | 1.5 mL/100 lb (10 mg/kg) | 3,356 head |

- Calves were housed in 250- or 300-head capacity, open-air, dirt-floor pens with concrete fence line feed bunks typical of feedlots in western Canada.
- Pens were observed at least once a day by experienced pen checkers. Animals deemed sick were moved to a hospital facility for assessment. Animal health personnel were blinded as to the experimental status of each pen
- A diagnosis of "undifferentiated fever" (UF) was made if:
  - there was an absence of abnormal clinical signs referable to organ systems other than the respiratory tract,
  - the calf had an elevated rectal temperature > 40.5°C (≥105.0°F),
  - there was no previous treatment history for no fever (NF), and
  - a period of at least three days had elapsed since allocation-and-arrival metaphylactic treatment.
- UF relapses were defined as calves returned to their original feedlot pen following initial UF therapy that were subsequently selected as "sick" by the pen checkers and exhibited respiratory signs.
- A diagnosis of "no fever" (NF) was made if:
  - there was an absence of abnormal clinical signs referable to organ systems other than the respiratory tract,
  - the calf had an elevated rectal temperature > 40.5°C (≤105.0°F),
  - there was no previous treatment history for NF, and
  - a period of at least three days had elapsed since allocation-and-arrival metaphylactic treatment.
- NF relapses were defined as calves returned to their original feedlot pen following initial UF therapy that were subsequently selected as "sick" by the pen checkers and exhibited respiratory signs.
- The treatment protocols used for UF and NF were identical and standardized for all experimental groups. Other diseases were treated and recorded as per the standard feedlot protocol.
- All animals that died were examined post mortem. The cause of death was determined for each animal by a veterinarian, based on the findings of the gross post-mortem examination.
- Animals from the experimental groups in each replicate were slaughtered on an equal days-on-feed basis.

## Results

### Health Outcomes

There were no statistical differences between Zuprevo and Draxxin in the health outcomes. However, Zuprevo-treated calves had a significantly lower first UF treatment rate, lower overall mortality and fewer death losses due to histophilosis than did Micotil-treated calves.

| Animal Health Variable Morbidity | Zuprevo | Draxxin | Micotil | P-value Zuprevo vs. Draxxin | P-value Zuprevo vs. Micotil |
|---|---|---|---|---|---|
| First UF Treatment | 7.00% | 7.02% | 15.07% | 0.918 | <0.001 |
| First UF Relapse | 23.16% | 20.66% | 23.70% | 0.568 | 0.971 |
| First NF Treatment | 4.36% | 3.75% | 5.38% | 0.365 | 0.202 |
| First NF Relapse | 20.05% | 17.44% | 22.03% | 0.221 | 0.657 |
| Chronicity† | 3.05% | 2.49% | 3.13% | 0.226 | 0.809 |
| Wastage†† | 2.31% | 2.01% | 2.45% | 0.499 | 0.688 |

†Chronicity is the number of animals with chronic disease (all causes) divided by the number of animals allocated.

††Wastage is the number of animals with chronic disease (all causes) that did not die divided by the number of animals allocated.

| Animal Health Variable Morbidity | Zuprevo | Draxxin | Micotil | P-value Zuprevo vs. Draxxin | P-value Zuprevo vs. Micotil |
|---|---|---|---|---|---|
| Overall Mortality | 2.50% | 2.03% | 3.03% | 0.273 | 0.020 |
| BRD Mortality | 0.54% | 0.43% | 0.87% | 0.363 | 0.157 |
| BVD/Enteritis | 0.06% | 0.03% | 0.03% | 0.571 | 0.327 |
| Histophilosis | 0.35% | 0.28% | 0.67% | 0.720 | 0.034 |
| Lameness | 0.21% | 0.12% | 0.14% | 0.293 | 0.226 |
| Metabolic | 0.57% | 0.54% | 0.49% | 0.866 | 0.390 |
| Other | 0.60% | 0.51% | 0.62% | 0.655 | 0.999 |

## Performance Outcomes and Carcass Traits

### Health Outcomes

There were no statistical differences between Zuprevo and Draxxin in the health outcomes. However, Zuprevo-treated calves had a significantly lower first UF treatment rate, lower overall mortality and fewer death losses due to histophilosis than did Micotil-treated calves.

| Feedlot Performance Variable | Zuprevo | Draxxin | Micotil | Standard Error | P-value Zuprevo vs. Draxxin | P-value Zuprevo vs. Micotil |
|---|---|---|---|---|---|---|
| **Average Daily Gain (lb/day)** | | | | | | |
| Live Weight Basis | 3.13 | 3.14 | 3.13 | ±0.03 | 0.685 | 0.960 |
| Carcass Weight Basis | 3.26 | 3.27 | 3.26 | ±0.02 | 0.788 | 0.956 |
| **Dry Matter Intake to Gain Ratio** | | | | | | |
| Live Weight Basis | 6.41 | 6.48 | 6.44 | ±0.06 | 0.162 | 0.595 |
| Carcass Weight Basis | 6.16 | 6.20 | 6.19 | ±0.03 | 0.325 | 0.494 |

| Carcass Variable | Zuprevo | Draxxin | Micotil | Standard Error | P-value Zuprevo vs. Draxxin | P-value Zuprevo vs. Micotil |
|---|---|---|---|---|---|---|
| **Yield Grades** | | | | | | |
| Yield Grade 1 | 71.98% | 67.73% | 68.40% | ±2.23% | 0.003 | 0.009 |
| Yield Grade 2 | 22.06% | 25.32% | 25.68% | ±1.74% | 0.013 | 0.008 |
| Yield Grade 3 | 5.95% | 6.95% | 5.92% | ±0.64% | 0.155 | 0.959 |
| **Dry Matter Intake to Gain Ratio** | | | | | | |
| Prime | 0.19% | 0.21% | 0.12% | ±0.05% | 0.765 | 0.404 |
| AAA | 37.38% | 41.01% | 40.07% | ±2.09% | 0.102 | 0.212 |
| AA | 58.21% | 55.10% | 55.61% | ±1.82% | 0.107 | 0.170 |
| A | 3.38% | 2.46% | 3.15% | ±0.56% | 0.073 | 0.631 |

### Health Outcomes

Zuprevo is the newest long-acting macrolide product on the market for the reduction of morbidity, when administered on arrival to feedlot calves at high risk of developing bovine respiratory disease. In this study, Zuprevo is proven to be effective.



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# ZUPREVO™ 18%

## *(Tildipirosin)*

Injectable Solution for Cattle

**ANTIMICROBIAL DRUG:**
180 mg of tildipirosin/mL

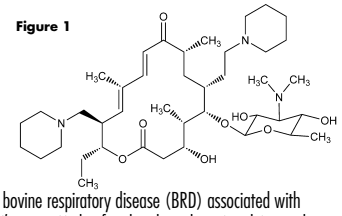
For subcutaneous injection in beef and non-lactating dairy cattle only. Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

**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

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