technical bulletin

Comparison of Resflor Gold® (florfenicol and flunixin meglumine) and Draxxin® (tulathromycin) in Treatment of Bovine Respiratory Disease in a California Calf Ranch

Abstract: In May 2010, a randomized clinical trial was initiated to examine the health performance differences between RESFLOR GOLD (florfenicol and flunixin meglumine) and Draxxin (tulathromycin) in a California calf ranch. In this 35-day study, Holstein steers (n = 921), were assessed for BRD in group pens after leaving hutches, with a pair of pens filled during a 4-day or less period. A total of 694 animals qualified for the study and were treated with RESFLOR GOLD (n=349) or Draxxin (n=345), according to the randomly allocated treatment for each pen in a pair of pens, with both using a 5-day post treatment interval. The overall incidence of BRD in this study was 75% (694/921). The first treatment success rate of 94.3% (329/349) for RESFLOR GOLD was not significant (p= 0.11) to Draxxin's 90.7% (313/345) for cattle in this study. The second treatment success rate with NUFLOR GOLD as the second treatment were 75% (15/20) for the RESFLOR GOLD treatment group and 75% (24/32) for the Draxxin treatment group (p= 0.99). There were no mortalities during this 35-day study.

Study Animals

- 921 Holstein steers were eligible for inclusion
- 694 Holstein steers qualified for the study
- Animals weighed 185-215 lbs body weight
- Deemed by study veterinarian to be at high risk for developing BRD

Study Design

- Timing: Feb. 23-April 12, 2010
- Randomized, blinded
- Natural BRD clinical trial
- Trial duration: 49 days
- Location: California calf ranch
- Study done in group pens

Enrollment Criteria

Animals exhibiting clinical signs of BRD were enrolled; in addition, depression and respiratory scores were assigned to each enrollee.

Depression Scores

0 = Normal: Bright, alert and responsive
1 = Mildly depressed
2 = Moderately depressed
3 = Severely depressed

Respiratory Scores

0 = Normal: No abnormal respiratory symptoms
1 = Mild respiratory distress
2 = Moderate respiratory distress
3 = Severe respiratory distress

Treatments and Dosing

The initial treatments for this study were:

1. RESFLOR GOLD: 40 mg/kg florfenicol : 2.2 mg/kg flunixin meglumine (6 mL/cwt), SQ in the neck one time with a 5-day PTI (post treatment interval).
2. Draxxin: 2.5 mg/kg (1.1 mL/cwt), SQ in the neck one time with a 5-day PTI.

Outcomes

- Morbidity
- First treatment success rate
- Mortality

Results and Discussion

Average Depression and Respiratory Scores at Enrollment

- Average Depression Scores: Draxxin (2.09); RESFLOR GOLD (2.11); p = 0. 41
- Average Respiratory Scores: Draxxin (1.50); RESFLOR GOLD (1.51); p = 0.66

Average BRD Incidence (Morbidity)

- The overall incidence of BRD in the candidate population was 75.35% (694/921)
- The range of BRD incidence within pens was 66.7%-87.1%
- Overall RESFLOR GOLD treatment group: 349/446 = 78.25%
- Overall Draxxin treatment group: 345/475 = 72.63%

Trial Results Summary

Pen Allocation and Treatment Success of Holstein Steer Calves Eligible to be Treated with Either RESFLOR GOLD or Draxxin for BRD

Treatment	Pen Number	Head Count	Calves with BRD	First Treatment Success (#) After 5-day PTI	First Treatment Success Rate (%)
RESFLOR GOLD	63	82	64	62	96.88%
Draxxin	64	87	58	56	96.55%
RESFLOR GOLD	65	88	60	58	96.67%
Draxxin	66	99	77	73	94.81%
RESFLOR GOLD	67	100	81	77	95.06%
Draxxin	68	94	69	60	86.96%
RESFLOR GOLD	69	83	63	57	90.48%
Draxxin	70	99	72	63	87.50%
RESFLOR GOLD	71	93	81	75	92.59%
Draxxin	72	96	69	61	88.41%

Treatment Success (Figure 1)

- First treatment success of 94.3% (329/349) for RESFLOR GOLD was not significant (p= 0.11) to Draxxin's 90.7% (313/345). See Table 1.
- Second treatment success rate with NUFLOR GOLD as the second treatment was 75% (15/20) for the RESFLOR GOLD treatment group and 75% (24/32) for the Draxxin treatment group (p= 0.99) See Table 2.

Mortality: There were no mortalities during this 35-day study.

Conclusion: In this field trial RESFLOR GOLD'S average first treatment success rate of 94.3% was not significantly different (p= 0.11) when compared to Draxxin's average first treatment success rate of 90.7% for BRD. There was no significant difference in the average respiratory scores 1.50 (Draxxin) and 1.51 (RESFLOR GOLD) or the average depression scores 2.09 (Draxxin) and 2.11 (RESFLOR GOLD) of animals enrolled in this study.

Table 1

First Treatment Success Rate for Cattle Treated for BRD with RESFLOR GOLD or Draxxin

	Success (#)	Fail (#)	Totals	First Treatment Success Rate (%)
RESFLOR GOLD	329	20	349	94.3%
Draxxin	313	32	345	90.7%
Totals	642	52	694	

Table 2

Second Treatment Success Rate for Cattle in both Groups Treated for BRD with NUFLOR GOLD

	Success (#)	Fail (#)	Totals	Second Treatment Success Rate (%)
RESFLOR GOLD	15	5	20	75.0
Draxxin	24	8	32	75.0
Totals	39	13	52	

Do not use in animals that have shown hypersensitivity to florfenicol or flunixin. Do not use in female dairy cattle 20 months of age or older or in calves to be processed for veal. For withdrawal period, adverse reactions, user safety and complete directions for use, see packaging insert.

PRODUCT INFORMATION
NADA 141-299, Approved by FDA.

Resflor GOLD
Florfenicol and Flunixin Meglumine

(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 nonsteroidal antiinflammatory 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 500mL vial, do not puncture the stopper more than 10 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

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

Recommended Injection Location

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, concominant use of RESFLOR GOLD® with other antiinflammatory 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 tocolytic 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. 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 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.

In cattle, rare instances of anaphylactic-like reactions, some of which have been fatal, have been reported, primarily following intravenous use of flunixin meglumine.

CLINICAL PHARMACOLOGY:
The pharmacokinetics (PK) of florfenicol (Table 1) and flunixin (Table 2) after subcutaneous injection of RESFLOR GOLD® is described below:

Table 1. Mean (n=28) pharmacokinetic parameters for florfenicol in cattle after a single subcutaneous administration of RESFLOR GOLD (florfenicol dose of 40 mg/kg BW).

Mean Florfenicol PK parameters in Cattle						
PK Parameter	AUC_{0-t} [1] (ng*hr/mL)	AUC_{0-inf} [2] (ng*hr/mL)	C_{max} [3] (ng/mL)	T_{max} [4] (hr)	$T_{½}$ [5] (hr)	MRT_{0-inf} [6] (hr)
Mean	242527	247577	11151	6.25	28.5	27.3
SD[7]	42741	41391	4194	3.87	9.91	11.6

Table 2. Mean (n=28) pharmacokinetic parameters for flunixin in cattle after a single subcutaneous administration of RESFLOR GOLD (flunixin dose of 2.2 mg/kg BW).

Mean Flunixin PK parameters in Cattle						
PK Parameter	AUC_{0-t} [1] (ng*hr/mL)	AUC_{0-inf} [2] (ng*hr/mL)	C_{max} [3] (ng/mL)	T_{max} [4] (hr)	$T_{½}$ [5] (hr)	MRT_{0-inf} [6] (hr)
Mean	13370	14448**	1913	1.14	9.5**	11.4
SD[7]	4964	5116	791	0.97	3.27	4.41

[1] AUC_{0-t} = Area under the plasma-concentration-time curve (AUC) from time zero to the last quantifiable concentrations
[2] AUC_{0-inf} = AUC from time zero to infinity
[3] C_{max} = Maximum plasma concentration
[4] T_{max} = Time at which Cmax was observed
[5] $T_{½}$ = Terminal elimination half-life
[6] MRT_{0-inf} = Mean residence time from time zero to infinity
[7] SD = Standard deviation
** n=27

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 BRD pathogens *M. haemolytica*, *P. multocida*, *H. somni* and *M. bovis* and that florfenicol exhibits bactericidal activity against strains of *M. haemolytica* and *H. somni*.

The minimum inhibitory concentrations (MICs) of florfenicol were determined for BRD isolates obtained from calves enrolled in BRD field studies in the U.S. in 2006 using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). Isolates were obtained from pre-treatment nasal swabs from all calves enrolled at all four sites, post-treatment nasal swabs from treatment failures in the RESFLOR GOLD and saline control treatment groups at three sites, and lung tissue from one calf that died in the saline control treatment group. The results are shown in Table 3.

Table 3. Florfenicol MIC values* of indicated pathogens isolated from cattle with naturally-ocurring BRD.

Indicated pathogens	Year of isolation	Number of isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	2006	183	1.0	1.0	0.5 to 32
Pasteurella multocida	2006	139	0.5	0.5	≤ 0.125 to 16
Histophilus somni	2006	84	≤ 0.125	≤ 0.125	≤ 0.125 to 0.25

* 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-site field study, calves with naturally occurring BRD were treated with RESFLOR GOLD®, Nuflor Gold® (NADA 141-265), or saline. A treatment success was defined as a calf with normal respiration to mild respiratory distress, normal attitude to mildly depressed, and a rectal temperature < 104.0 °F on Day 11.

The treatment success rate for BRD for the RESFLOR GOLD® treatment group (68.4%) was statistically significantly greater (p = 0.0255) compared to the saline control treatment group (42.9%). RESFLOR GOLD® was non-inferior to Nuflor Gold® for the treatment of BRD, with a one-sided 95% lower confidence bound for the difference between the two treatments equal to -13.2%.

In the same study, the change in rectal temperature from pre-treatment to six hours post-treatment was evaluated to determine the effectiveness of RESFLOR GOLD® for the control of BRD-associated pyrexia. The proportion of calves whose rectal temperatures decreased by ≥ 2.0 °F from pre-treatment to six hours post-treatment was statistically significantly greater (p = 0.0019) in the RESFLOR GOLD® treatment group compared to the saline control treatment group. The mean decrease in rectal temperature from pre-treatment to six hours post-treatment was statistically significantly greater in the RESFLOR GOLD® treatment group compared to the Nuflor Gold® and saline control treatment groups (p = 0.0031 and 0.0002, respectively).

The effectiveness of RESFLOR GOLD for the treatment of BRD associated with *Mycoplasma bovis* was demonstrated by examining the *M. bovis* data from cattle enrolled in the BRD treatment study described above. There were numerically more treatment successes (6 of 8 calves, 75%) than treatment failures (2 of 8 calves, 25%) in RESFLOR GOLD-treated calves that cultured positive for *M. bovis* pre-treatment.

ANIMAL SAFETY: A target animal safety study was conducted to evaluate the effects of RESFLOR GOLD® when administered to cattle subcutaneously at 1X, 3X, or 5X the labeled dose for three consecutive days (3X the labeled duration). Decreased feed and water consumption, and decreased body weights (secondary to decreased feed consumption) were observed in the 1X, 3X, and 5X groups. Injection site swellings were noted in the 1X, 3X, and 5X groups.

A separate injection site study was conducted in cattle. The study demonstrated that RESFLOR GOLD®, when administered according to the label directions, may induce a transient local reaction in the subcutaneous and underlying muscle tissue.

STORAGE INFORMATION: Do not store above 30°C (86°F). Use within 28 days of first use.

HOW SUPPLIED: RESFLOR GOLD® is available in 100, 250, and 500 mL sterile, multiple-dose, glass vials.

Made in Germany
Intervet Inc. Roseland, NJ 07068

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