Resflor GOLD Florfenicol and Flunixin Meglumine

TECH BULLETIN

MERCK Animal Health

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

Key Highlights

- 655 Holstein steers exhibiting clinical signs of BRD were randomly treated with Resflor Gold or Baytril using a five-day post-treatment interval.
- First treatment success rate of 91% for Resflor Gold is significant ($p<0.0001$) to 79% for Baytril in this study.
- Resflor Gold with a five-day post-treatment interval outperformed Baytril as a first treatment antibiotic for bovine respiratory disease.

ABSTRACT

In February 2010, a randomized, blinded clinical trial to examine the health performance differences between Resflor Gold® (florfenicol and flunixin meglumine) and Baytril® (enrofloxacin) in a California calf ranch was initiated. In this 49-day study, Holstein steers were assessed for BRD in group pens after leaving hutches. A total of 655 animals qualified for the study and were randomly treated with Resflor Gold (n=322) or Baytril (n=333), and both used a five-day post-treatment interval. The overall incidence of BRD in this study was 46% (655/1410). The first treatment success rate 91% (293/322) for Resflor Gold is significant ($p<0.0001$) to Baytril 79% (262/333) for cattle in this study. There were no mortalities during this 49-day study. This study shows that Resflor Gold (with a five-day post-treatment interval) outperformed Baytril in initial BRD treatment success.

STUDY ANIMALS

- 655 Holstein steers were eligible for inclusion
- Animals were 185 - 215 lbs body weight
- Deemed by study veterinarian to be at high risk for developing BRD
- All animals were PI-BVD negative

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 five-day PTI (post-treatment interval)
2. Baytril: 11 mg/kg (5 mL/cwt), SQ in the neck one time with a five-day PTI.

OUTCOMES

- Morbidity
- First treatment success rate
- Mortality

RESULTS AND DISCUSSION

AVERAGE DEPRESSION AND RESPIRATORY SCORES AT ENROLLMENT

- Average Depression Scores: Baytril (2.26); Resflor Gold (2.3); $p = 0.29$
- Average Respiratory Score: Baytril (1.79); Resflor Gold (1.83); $p = 0.40$

AVERAGE BRD INCIDENCE (MORBIDITY)

- The overall incidence of BRD in the candidate population was 46% (655/1410)
- The range of BRD within pens was 15% - 93%
- Overall Resflor Gold treatment group: 322/678 = 47%
- Overall Baytril treatment group: 333/732 = 45%

Pen Allocation and Treatment Success of Holstein Steer Calves Eligible to be Treated with Either Resflor Gold or Baytril for BRD

Treatment	Pen Number	Head Count	Calves with BRD	First Treatment Success (#) After Five-Day PTI	First Treatment Success Rate (%)
Resflor Gold	23	84	39	33	84.62%
Baytril	24	89	51	41	80.39%
Resflor Gold	25	87	31	29	93.55%
Baytril	26	107	36	29	80.56%
Resflor Gold	27	88	39	31	79.49%
Baytril	28	83	40	31	77.50%
Resflor Gold	29	80	25	24	96.00%
Baytril	30	84	21	18	85.71%
Resflor Gold	31	79	15	14	93.33%
Baytril	32	104	16	14	87.50%
Resflor Gold	74	90	51	45	88.24%
Baytril	73	100	45	34	75.56%
Resflor Gold	76	100	57	54	94.74%
Baytril	75	100	65	49	75.38%
Resflor Gold	78	70	65	63	96.92%
Baytril	77	65	59	46	77.97%

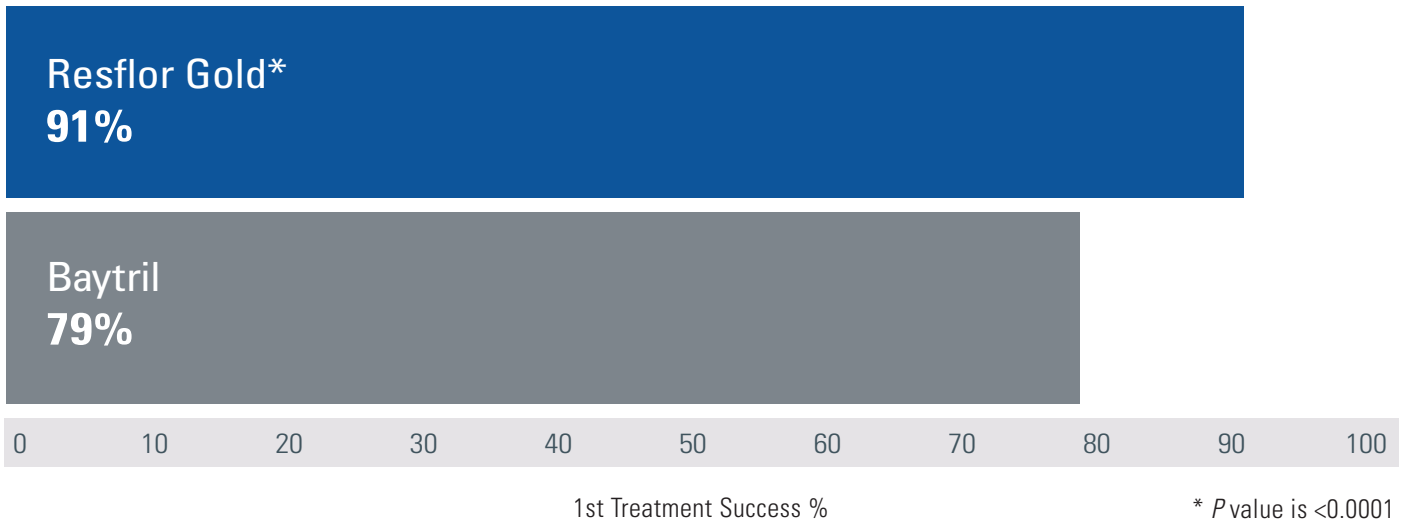
TREATMENT SUCCESS (FIGURE 1)

- First treatment success rate 91% (293/322) for Resflor Gold is significant ($p<0.0001$) to Baytril 79% (262/333)

MORTALITY

- There were no mortalities during this 49-day study.

FIGURE 1. FIRST TREATMENT SUCCESS RATE FOR CATTLE TREATED FOR BRD WITH RESFLOR GOLD OR BAYTRIL



CONCLUSION

In this field trial, Resflor Gold (with a five-day post-treatment interval) outperformed Baytril as a first treatment antibiotic for bovine respiratory disease. There was no significant difference in the average respiratory scores 1.79 (Baytril) and 1.83 (Resflor Gold) or the average depression scores 2.26 (Baytril) and 2.30 (Resflor Gold) of animals enrolled in this study. Following initial antimicrobial treatment, a five-day post-treatment interval (PTI) was observed for all animals. During this time no animal was eligible for retreatment (unless moribund). The first treatment success rate for Resflor Gold was 91%, which is significant ($p<0.0001$) as compared to a first treatment success rate of 79% for Baytril. This study shows that Resflor Gold (with a five-day post-treatment interval) outperformed Baytril as an initial treatment for bovine respiratory disease.

IMPORTANT SAFETY INFORMATION: Animals intended for human consumption must not be slaughtered within 38 days 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. For more information, see packaging insert.

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PRODUCT INFORMATION
NADA 141-299, Approved by FDA.

122996 R3

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 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

* 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 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 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. 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.

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 C_{max} 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,* and *H. somni,* and *M. bovis* that florfenicol exhibits bactericidal activity against strains of *M. haemolytica* and *H. somni.*
The minimum inhibitory concentrations (MICs) of florfenicol were determined for non-mycoplasmal 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). MICs for *M. bovis* isolates were determined by an accepted method using Hayflick Broth with Alamar Blue (HBAN) medium under appropriate control. 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 below 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
Mycoplasma bovis	2006	60	1.0	1.0	0.5 to 1.0

* 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
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