Date of Approval: February 8, 2012

FREEDOM OF INFORMATION SUMMARY -

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-328

ZACTRAN

Gamithromycin
Injectable Solution
Beef and Non-Lactating Dairy Cattle -

For the treatment of bovine respiratory disease (BRD) associated with *Mycoplasma bovis* in beef and non-lactating dairy cattle

Sponsored by: -

Merial Ltd. -

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-328
B. Sponsor:	Merial Ltd. - 3239 Satellite Blvd., Bldg. 500 Duluth, GA 30096-4640 - Drug Labeler Code: 050604
C. Proprietary Name:	ZACTRAN
D. Established Name:	Gamithromycin
E. Pharmacological Category:	Antimicrobial
F. Dosage Form:	Injectable Solution
G. Amount of Active Ingredient:	150 mg gamithromycin/mL
H. How Supplied:	100, 250, and 500 mL bottles
I. How Dispensed:	Rx
J. Dosage:	6 mg/kg body weight (2 mL per 110 lb BW), administered one time
K. Route of Administration:	Subcutaneous injection in the neck
L. Species/Classes:	Cattle/Beef and non-lactating dairy
M. Indications:	ZACTRAN is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* **and *Mycoplasma bovis*** in beef and non-lactating dairy cattle. ZACTRAN is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida*.
N. Effect of Supplement:	This supplement provides for a new indication, "for the treatment of bovine respiratory disease (BRD) associated with *Mycoplasma bovis* in beef and non-lactating dairy cattle".

II. EFFECTIVENESS:

A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-328 dated June 16, 2011, contains dosage characterization information for beef and non-lactating dairy cattle.

B. Substantial Evidence:

The effectiveness of gamithromycin for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in beef and non-lactating dairy cattle was previously demonstrated in the original approval, and is summarized in the FOI Summary for ZACTRAN (NADA 141-328) dated June 16, 2011. The effectiveness of gamithromycin for the treatment of BRD associated with *Mycoplasma bovis* in beef and non-lactating dairy cattle was demonstrated in two separate natural infection field studies that used a similar study protocol and were evaluated independently.

Natural Infection Field Studies

1. - Title: "Field Efficacy Study of ML 1,709,460 Injectable Solution for the Treatment of Bovine Respiratory Disease Associated with Mycoplasma bovis in Beef and Non-lactating Dairy Cattle." Study PR&D 0170301 (November 2009) and Study PR&D 0170302 (March 2010 to April 2010).

2. - Investigators and Study Locations:

   PR&D 0170301: Kelly F. Lechtenberg, DVM, PhD, Central States Research Centre, Inc., Oakland, NE. -

   PR&D 0170302: C. Scanlon Daniels, DVM, Agri-Research, Inc., Canyon, TX. -

3. - Study Design:

   a) - *Objective:* To evaluate the effectiveness of ML-1,709,460 (gamithromycin) for the treatment of BRD associated with *M. bovis*.

   b) - *Study Animals*: Multi-origin, commingled, purebred and crossbred, male (intact and castrated) and female beef cattle weighing 160 to 286 kg were obtained from sale barns and transported less than 24 hours to the study sites. There were 502 animals enrolled in the study across both sites.

   c) - *Experimental Design*: Following arrival, a nasopharyngeal swab sample was collected from each candidate animal for determination (via culture) of *M. bovis* status. Animals were observed for the presence of BRD clinical signs for up to 5 days after presumptive *M. bovis* determination. Animals were enrolled if they exhibited clinical signs of BRD (depression score ≥ 2 and/or respiratory character score ≥ 2, AND rectal temperature ≥ 104.0 °F). All

eligible *M. bovis*-positive animals were enrolled, followed by enough *M. bovis*-negative animals to complete the target study enrollment.

Depression score was evaluated using the following criteria:

0 = normal (bright, alert, and responsive);
1 = mild depression (May stand isolated with its head down or ears drooping, but will quickly respond to minimal stimulation.);
2 = moderate depression (May stand isolated with its head down, it may show signs of muscle weakness [standing cross-legged or knuckling when walking]. Shows a delayed response to minimal stimulation or requires greater stimulation before showing a response.);
3 = severe depression (May be recumbent and reluctant to rise, or if standing isolated, may be reluctant to move. When moving, ataxia, knuckling, or swaying evident. Eyes dull, head carried low with ears drooping, possible excess salivation/lacrimation.);
4 = moribund (recumbent)

Respiratory character was evaluated using the following criteria:

0 = Normal (No abnormal respiratory symptoms present. Respiratory rate and effort were appropriate for the environment);
1 = Mild Respiratory Distress (serous nasal or ocular discharge and/or cough);
2 = Moderate Respiratory Distress (mucous or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort);
3 = Severe Respiratory Distress (marked increase in respiratory rate or effort including one or more of the following: open mouth breathing, abdominal breathing, or extended head)

At each site, enrolled cattle were randomly allocated to replicate and to treatment group by order of presentation at the restraint chute. Day 0 was the day of enrollment and was the same for each animal in a replicate. Replicate pairs of animals (one treated, one control) were penned together in pens containing up to five replicate pairs. The experimental unit was the animal. Personnel conducting post-treatment evaluations were masked to treatment assignments.

d) - Treatment Groups: Animals were assigned to one of two treatment groups as follows:

Table 1. Treatment Group Assignments, Studies PR&D 0170301 and PR&D 0170302.

Group	Treatment Regimen	PR&D 0170301	PR&D 0170302
1	gamithromycin, 6.0 mg/kg (2.0 mL/50 kg) body weight (BW)	121 animals	130 animals
2	saline, 2.0 mL/50 kg BW	121 animals	130 animals

e) - *Drug Administration*: The test article (gamithromycin injectable solution) and control article (sterile saline for injection) were administered by subcutaneous (SC) injection in the neck on the each animal's day of

enrollment (Day 0). A maximum of 10 mL was administered per injection site.

f) - *Measurements and Observations*: At the time of enrollment, an additional nasopharyngeal swab was collected for culture and polymerase chain reaction (PCR) testing for *M. bovis*. Enrolled animals were observed daily for animal health and scored for BRD clinical signs from Days 1 through 10. Animals with severe BRD (respiratory or depression scores ≥ 3) on Days 1 through 10 were removed and classified as treatment failures. Rectal temperatures were recorded for all animals remaining in the study on Day 10. Animals that remained in the study and had a depression score ≤ 1, a respiratory character score ≤ 1, and a rectal temperature < 104 °F on Day 10 were considered a treatment success.

Animals in the gamithromycin-treated group that were declared treatment successes and were in the subset of animals positive for *M. bovis* from the Day 0 pre-treatment swab sample (by culture results and confirmed by PCR) were considered treatment successes for BRD associated with *M. bovis*.

4. - Statistical Analysis: Each site was evaluated independently for overall BRD treatment success. The proportion of treatment successes in the gamithromycin-treated and saline-treated groups was analyzed using a generalized linear mixed model with a logit link function. Treatment was the fixed effect, and pen and pen-by-treatment interaction were the random effects. A two-sided test was used at the significance level of 0.05.

5. - Results: One animal was removed from the analysis because of a significant protocol deviation.

a) - *Overall Treatment Success*:

PR&D 0170301 - The percentage of animals classified as a treatment success was statistically significantly higher ($p < 0.001$) in the gamithromycin-treated group (90/121, 74.4%) compared to the control group (29/121, 24.0%).

PR&D 0170302 - The percentage of animals classified as a treatment success was statistically significantly higher ($p = 0.002$) in the gamithromycin-treated group (87/129, 67.4%) compared to the control group (60/130, 46.2%).

b) - *M. bovis Treatment Success*:

PR&D 0170301 - 57 animals in the gamithromycin-treated group were positive for *M. bovis* based on culture and PCR confirmation of the pre-treatment samples. Of those animals, 45 (79.0%) were treatment successes on Day 10.
PR&D 0170302 - 6 animals in the gamithromycin-treated group were positive for *M. bovis* based on culture and PCR confirmation of the pre-treatment samples. Of those animals, 5 (83.3%) were treatment successes on Day 10.

6. - Adverse Events: No test article-related adverse events were observed.

7. - Conclusions: Gamithromycin is effective for the treatment of BRD associated with *M. bovis* when administered to beef and non-lactating dairy cattle as a SC injection of 6 mg/kg BW given one time.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-328 dated June 16, 2011, contains a summary of target animal safety studies for beef and non-lactating dairy cattle.

IV. HUMAN FOOD SAFETY:

A. Microbial Food Safety (Antimicrobial Resistance):

The impact of the proposed addition of a pathogen, *Mycoplasma bovis*, to the approved indication for gamithromycin for the treatment of bovine respiratory disease in beef and non-lactating dairy cattle was carefully considered by the Agency. The Agency determined that because there are no changes in formulation, dosage, route of administration, or duration of use in this supplement, the addition of an additional pathogen to the approved treatment indication should not significantly impact public health. The Agency did not require any additional information for microbial food safety (antimicrobial resistance) for this supplemental approval. The FOI Summary for the original approval of NADA 141-328 dated June 16, 2011, contains a summary of all information used to assess microbial food safety (antimicrobial resistance) risks.

B. Impact of Residues on Human Intestinal Flora:

CVM did not require additional information for the impact of gamithromycin residues on human intestinal flora for this supplemental approval. The FOI Summary for the original approval of NADA 141-328 dated June 16, 2011, contains a summary of all information used to assess the impact of residues on human intestinal flora.

C. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-328 dated June 16, 2011, contains a summary of all pivotal toxicology studies.

D. Assignment of the Final Acceptable Daily Intake (ADI):

No reassessment of the toxicological ADI, microbiological ADI, or toxicological acceptable single dose intake (ASDI) was needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-328 dated June 16, 2011, contains a summary of all toxicology studies and information used to assess the impact of residues on human intestinal flora.

E. Safe Concentrations for Total Residues (edible tissues and injection sites, if applicable):

No reassessment of the safe concentrations for total residues was needed for this supplemental approval. The FOI Summary for the original approval of

NADA 141-328 dated June 16, 2011, contains a summary of all toxicology studies and microbial food safety studies.

F. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-328 dated June 16, 2011, contains a summary of residue chemistry studies for beef and non-lactating dairy cattle.

G. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-328 dated June 16, 2011, contains the analytical method summaries for gamithromycin in beef and non-lactating dairy cattle.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ZACTRAN:

For use in cattle only. Not for use in humans. Keep this and all drugs out of reach of children. The material safety data sheet (MSDS) contains more detailed occupational safety information. To report adverse effects, obtain an MSDS or for assistance, contact Merial at 1-888-637-4251.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that ZACTRAN, when used according to the label, is safe and effective for the treatment of BRD associated with *M. bovis* in beef and non-lactating dairy cattle. Additionally, data demonstrate that residues in food products derived from cattle treated with ZACTRAN will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). This decision was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat and control BRD, and (b) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

B. Exclusivity:

ZACTRAN qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the act. The three years of marketing exclusivity applies only to the indication for the treatment of BRD associated with *M. bovis*, for which this supplement is approved.

C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.