

BRD treatment and control field trials for ZACTRAN[®] (gamithromycin).

Reprints of the published treatment and control field studies and ZACTRAN package insert are enclosed. Contact your Merial Representative or Veterinary Professional Services for more information.

“Because it’s critical, it’s **ZACTRAN** *”*[™]
(gamithromycin)[®]

ZACTRAN® (gamithromycin) is structurally different.^{1*}

ZACTRAN is a novel subclass of macrolide with a structural difference. In pharmacokinetic and pharmacodynamic studies, the patented active ingredient in ZACTRAN, gamithromycin, demonstrated rapid absorption, extensive distribution in lung tissue and extended persistence at high levels in lung tissue.^{1,2*}

* Clinical relevance has not been determined.

Based on these favorable characteristics, ZACTRAN was placed in real-world field trials in cattle in commercial feedyards to determine the clinical efficacy for bovine respiratory disease (BRD) treatment and control.

Treatment study design.³

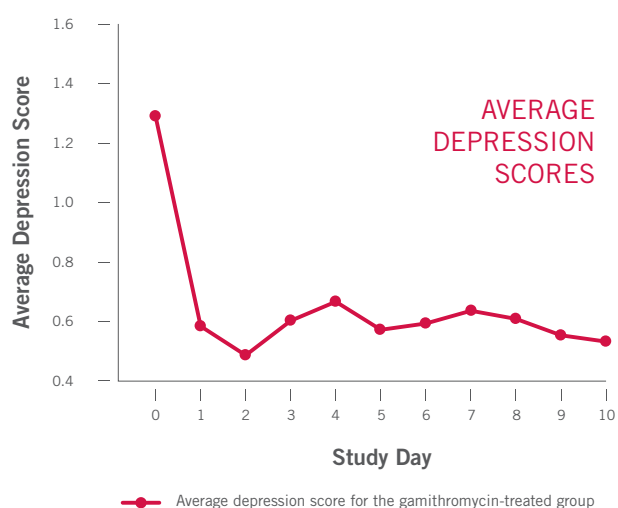
As part of the FDA approval process, four field trials evaluated administration of ZACTRAN as treatment in feeder cattle displaying clinical signs of BRD. Trials were conducted at four sites with a total of 498 beef calves (286 lbs. to 576 lbs).

The animals were trucked between 4 and 19.5 hours to study sites, processed upon arrival and placed in pens. Within three days post-arrival, if calves displayed clinical signs of BRD (depression score ≥ 1 , respiratory character score ≥ 1 , rectal temperature ≥ 40 °C/104 °F), they were enrolled in the study and received a single subcutaneous (SC) injection of ZACTRAN at 6 mg/kg (2 mL/110 lbs.). The study duration was 10 days.

Cattle treated with ZACTRAN responded within 24 hours.³

Clinically ill cattle that received an SC injection of ZACTRAN at the labeled dose of 2 mL/110 lbs. showed a rapid improvement in BRD clinical signs.³ In cattle treated with ZACTRAN, 76.5% with a rectal temperature above 104 °F experienced a significant decrease in temperature within 24 hours post-treatment.⁴

Cattle treated with ZACTRAN had decreased average depression scores.³



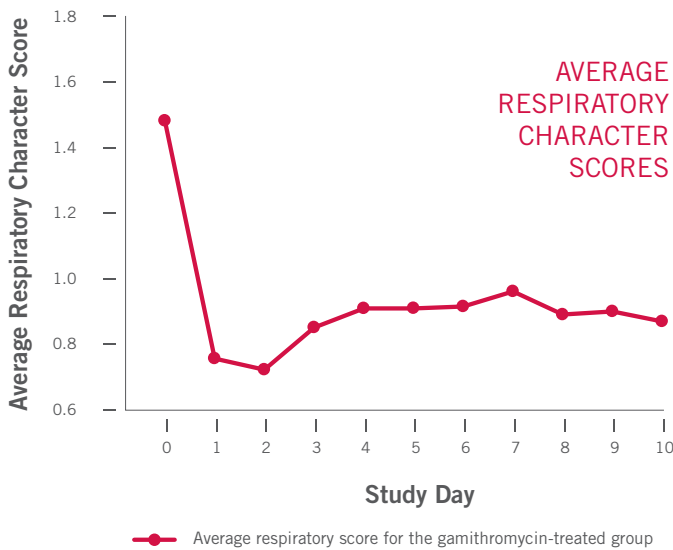
Results

Average depression scores for ZACTRAN-treated cattle decreased from a score of 1.3 to 0.6 within 24 hours post treatment.³

On each of the 10 days, cattle that received ZACTRAN had low average depression scores.³

IMPORTANT SAFETY INFORMATION: For use in cattle only. Do not treat cattle within 35 days of slaughter. Because a discard time in milk has not been established, do not use in female dairy cattle 20 months of age or older, or in calves to be processed for veal. The effects of ZACTRAN on bovine reproductive performance, pregnancy and lactation have not been determined.

Cattle treated with ZACTRAN® (gamithromycin) had decreased average respiratory character scores.³



Results

Average respiratory character scores of ZACTRAN-treated cattle decreased from 1.5 to 0.7 in the first 24 hours post-treatment.³

Cattle that received ZACTRAN had low average respiratory character scores from Day 1 through Day 10.³

Cattle treated with ZACTRAN stayed healthy for the 10-day study.³

Results from this BRD treatment study showed clinically ill cattle treated with ZACTRAN had low average depression scores, respiratory character scores and rectal temperatures over the 10 days of the study.³

BRD control in high-risk cattle.

Study design

Sale barn calves (68 bulls and 91 steers) were purchased in Kentucky and Tennessee and transported to Study Site 1 in Nebraska. Researchers sourced 308 heifers from livestock markets in Arkansas and transported them to Study Site 2 in Texas. A total of 467 lightweight calves (286-645 lbs.) were enrolled in the blinded studies.

On arrival, calves were processed with a viral respiratory vaccine and endectocide, and randomly

assigned to a ZACTRAN group (ZACTRAN SC at 2 mL/110 lbs.) or to a negative saline control group (saline SC at 2 mL/110 lbs.).

ZACTRAN controlled BRD for the 10-day study in long-haul, high-risk cattle.⁵

Significantly ($P < 0.05$) more cattle given ZACTRAN remained healthy for the entire 10-day study versus cattle given saline.⁵ Based on the results of these clinical field trials, ZACTRAN demonstrated effectiveness ($P < 0.05$) at controlling BRD in long-haul, high-risk cattle for the 10-day study.⁵

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Indications⁶

ZACTRAN[®] (gamithromycin) 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*.



Trade Name	ZACTRAN [®]
FDA Approval	NADA 141-328
Active Ingredient	Gamithromycin
Antimicrobial Class	Macrolide
Subclass	Azalide
Formulation	150 mg/mL
Dosage	6 mg/kg
Injection Volume	2 mL/110 lbs. (1 mL/25 kg)
Low Plasma Binding ^{6*}	26%
High Available Free Drug ^{6*}	74%
Bioavailability ^{1*}	Complete
High Volume of Distribution ^{6*}	25 L/kg
BRD Treatment Duration ³	10 days
BRD Control Duration ⁵	10 days
Rapid Treatment Response ³	24 hours

ZACTRAN is available in 500, 250 and 100 mL sizes.

* Clinical relevance has not been determined.

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¹ Giguere S, Huang R, Malinski TJ, et al. Disposition of gamithromycin in plasma, pulmonary epithelial lining fluid, bronchoalveolar cells and lung tissue in cattle. *Am J Vet Res.* 2011;72(3):326-330.

² Huang RA, Letendre LT, Banav N, et al. Pharmacokinetics of gamithromycin in cattle with comparison of plasma and lung tissue concentrations and plasma antibacterial activity. *J Vet Pharmacol Ther.* 2010;33(3):227-237.

³ Sifferman RL, Wolff WA, Holste JE, et al. Field efficacy evaluation of gamithromycin for treatment of bovine respiratory disease in cattle at feedlots. *Intern J Appl Res Vet Med.* 2011;9(2):189-197.

⁴ Data on file at Merial.

⁵ Lechtenberg K, Daniels CS, Royer, GC, et al. Field efficacy study of gamithromycin for the control of bovine respiratory disease in cattle at high risk of developing the disease. *Intern J Appl Res Vet Med.* 2011;9(2):171-180.

⁶ ZACTRAN product label approval in 2011.

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NADA 141-328



150 mg/mL ANTIMICROBIAL

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.

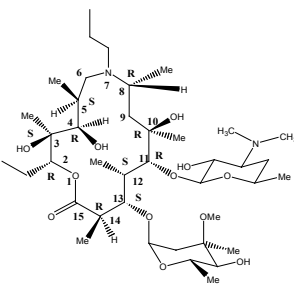
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
READ ENTIRE BROCHURE CAREFULLY BEFORE USING THIS PRODUCT.

DESCRIPTION

ZACTRAN® Injection for Cattle is a ready to use sterile parenteral solution containing gamithromycin, a macrolide sub-class, 7a-azalide antimicrobial. Each mL of ZACTRAN contains 150 mg of gamithromycin as the free base, 1 mg of monoethioglycerol and 40 mg of succinic acid in a glycerol formal vehicle.

The chemical name of gamithromycin is 1-Oxa-7-azacyclopentadecan-

15-one, 13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-7-propyl-11-[(3,4,6-trideoxy-3-(dimethylamino)-beta-D-xylo-hexopyranosyl)oxy]-, [(2R*, 3S*, 4R*, 5S*, 8R*, 10R*, 11R*, 12S*, 13S*, 14R*)]-and the structure is shown below.



INDICATIONS

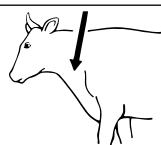
ZACTRAN is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* in beef and non-lactating dairy cattle. ZACTRAN is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

DOSAGE and ADMINISTRATION

Administer ZACTRAN one time as a subcutaneous injection in the neck at 6 mg/kg (2 mL/110 lb) body weight (BW). If the total dose exceeds 10 mL, divide the dose so that no more than 10 mL is administered at each injection site.

Body Weight (lb)	Dose Volume (mL)
110	2
220	4
330	6
440	8
550	10
660	12
770	14
880	16
990	18
1100	20

Animals should be appropriately restrained to achieve the proper route of administration. Use sterile equipment. Inject under the skin in front of the shoulder (see illustration).



CONTRAINDICATIONS

As with all drugs, the use of ZACTRAN is contraindicated in animals previously found to be hypersensitive to this drug.

WARNING:

**FOR USE IN CATTLE ONLY.
NOT FOR USE IN HUMANS.
KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.
NOT FOR USE IN CHICKENS OR TURKEYS.**

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.

RESIDUE WARNINGS: Do not treat cattle within 35 days of slaughter. Because a discard time in milk has not been established, do not use in female dairy cattle 20 months of age or older. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS

The effects of ZACTRAN on bovine reproductive performance, pregnancy, and lactation have not been determined. Subcutaneous injection of ZACTRAN may cause a transient local tissue reaction in some cattle that may result in trim loss of edible tissues at slaughter.

ADVERSE REACTIONS

Transient animal discomfort and mild to moderate injection site swelling may be seen in cattle treated with ZACTRAN.

CLINICAL PHARMACOLOGY

The macrolide antimicrobials as a class are weak bases and as such concentrate in some cells (such as pulmonary leukocytes). Prolonged exposure of extracellular pulmonary pathogens to macrolides appears to reflect the slow release of drug from its intracellular reservoir to the site of action, the pulmonary epithelial lining fluid (ELF). It is the ELF that is relevant to the successful treatment and control of BRD. Gamithromycin is primarily bacteriostatic at therapeutic concentrations. However, *in vitro* bactericidal activity has been observed at concentrations of 10 µg/mL (Mueller-Hinton broth) and after exposure to the 6-hour and 24-hour plasma samples derived from cattle dosed at 6 mg gamithromycin/kg BW. Macrolides typically exhibit substantially higher concentrations in the alveolar macrophages and ELF as compared to concentrations observed in plasma. Gamithromycin concentrations in the ELF and ELF cells exceed the concentrations observed in the plasma. Postmortem gamithromycin concentrations in ELF exceeded the MIC₅₀ of *M. haemolytica*, *H. somni* and *P. multocida* through at least 72 hours after drug administration. Because *M. haemolytica*, *P. multocida* and *H. somni* are extracellular pathogens, drug concentrations in the ELF are considered to be clinically relevant. The postmortem area under the concentration-time curve (AUC) observed in lysed ELF cells (e.g., alveolar macrophages) are at least 300-times greater than that in the plasma. Although published studies suggest that inflammation can increase the release of drug from macrophages and neutrophils, these high concentrations in the alveolar macrophages should not be considered indicative of the magnitude or duration of response to the pathogens for which this product is indicated.

ZACTRAN administered subcutaneously in the neck of cattle at a single dosage of 6 mg/kg BW is rapidly and completely absorbed, with peak concentrations generally occurring within 1 hour after administration. Based upon plasma and lung homogenate data, the terminal half-life (T_{1/2}) of gamithromycin is approximately 3 days. *In vitro* plasma protein binding studies show that 26% of the gamithromycin binds to plasma protein, resulting in free drug available for rapid and extensive distribution into body tissues. The free drug is rapidly cleared from the systemic circulation with a clearance rate of 712 mL/hr/kg and a volume of distribution of 25 L/kg. Dose proportionality was established based on AUC over a range of 3 mg/kg BW to 9 mg/kg BW. Biliary excretion of the unchanged drug is the major route of elimination.

MICROBIOLOGY

The minimum inhibitory concentrations (MICs) of gamithromycin were determined for BRD isolates obtained from calves enrolled in BRD treatment field studies in the U.S. in 2004 using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). Isolates were obtained from pre-treatment nasopharyngeal swabs from each enrolled calf and from calves removed from the study due to BRD. The results are shown below in Table 1.

Table 1. Gamithromycin minimum inhibitory concentration (MIC) values* of indicated pathogens isolated from BRD treatment field studies in the U.S.

Indicated Pathogens	Years of isolation	No. of isolates	MIC ₅₀ ** (µg/mL)	MIC ₉₀ ** (µg/mL)	MIC range (µg/mL)
<i>M. haemolytica</i>	2004	89	1	1	0.5 to >32
<i>P. multocida</i>	2004	79	0.5	1	0.12 to >32
<i>H. somni</i>	2004	32	0.5	0.5	0.25 to 1

* 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

The effectiveness of ZACTRAN for the treatment of BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* was demonstrated in a field study conducted at four geographic locations in the United States. A total of 497 cattle exhibiting clinical signs of BRD were enrolled in the study. Cattle were administered ZACTRAN (6 mg/kg BW) or an equivalent volume of sterile saline as a subcutaneous injection once on Day 0. Cattle were observed daily for clinical signs of BRD and were evaluated for clinical success on Day 10. The percentage of successes in cattle treated with ZACTRAN (58%) was statistically significantly higher (p<0.05) than the percentage of successes in the cattle treated with saline (19%).

The effectiveness of ZACTRAN for the treatment of BRD associated with *M. bovis* was demonstrated independently at two U.S. study sites. A total of 502 cattle exhibiting clinical signs of BRD were enrolled in the studies. Cattle were administered ZACTRAN (6 mg/kg BW) or an equivalent volume of sterile saline as a subcutaneous injection once on Day 0. At each site, the percentage of successes in cattle treated with ZACTRAN on Day 10 was statistically significantly higher than the percentage of successes in the cattle treated with saline (74.4% vs. 24% [p<0.001], and 67.4% vs. 46.2% [p = 0.002]). In addition, in the group of calves treated with gamithromycin that were confirmed positive for *M. bovis* (pre-treatment nasopharyngeal swabs), there were more calves at each site (45 of 57 calves, and 5 of 6 calves) classified as successes than as failures. The effectiveness of ZACTRAN for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida* was demonstrated in two independent studies conducted in the United States. A total of 467 crossbred beef cattle at high risk of developing BRD were enrolled in the study. ZACTRAN (6 mg/kg BW) or an equivalent volume of sterile saline was administered as a single subcutaneous injection within one day after arrival. Cattle were observed daily for clinical signs of BRD and were evaluated for clinical success on Day 10 post-treatment. In each of the two studies, the percentage of successes in the cattle treated with ZACTRAN (86% and 78%) was statistically significantly higher (p = 0.0019 and p = 0.0016) than the percentage of successes in the cattle treated with saline (36% and 58%).

ANIMAL SAFETY

In a target animal safety study in healthy, six-month old beef cattle, ZACTRAN was administered by subcutaneous injection at 6, 18, and 30 mg/kg bodyweight (1, 3, and 5 times the labeled dose) on Day 0, 5, and 10 (3 times the labeled administration frequency). Injection site discomfort (neck twisting, attempts to scratch or lick the injection site, and pawing at the ground) was observed in calves in the 18 mg/kg BW and 30 mg/kg BW groups at 10 minutes post-treatment following each injection. Mild to moderate injection site swelling and pathology changes consistent with inflammation were observed in the gamithromycin-treated groups. Other than injection site reactions, no clinically relevant treatment-related effects were observed.

STORAGE CONDITIONS

Store at or below 77°F (25°C) with excursions between 59-86°F (15-30°C). Use within 18 months of first puncture.

HOW SUPPLIED

ZACTRAN is available in three ready-to-use bottle sizes. The 100, 250 and 500 mL bottles contain sufficient solution that will treat 10, 25 and 50 head of 550 lb (250 kg) cattle respectively.

Marketed by Merial

3239 Satellite Blvd., Duluth, GA 30096-4640 U.S.A.

Made in Austria

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