
HIS HEAD IS DOWN.
HE'S CLEARLY STRESSED.
DON'T WORRY YOURSELF SICK ABOUT BRD.
"Because it's critical, it's
ZACTRAN™
(gamithromycin)

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ZACTRAN™
(gamithromycin)®

Rapid response in 24 hours[1]

10-day treatment and control with a single injection[1,2]

A real alternative for BRD

Ask your veterinarian about prescription ZACTRAN.

BRD HAS A BIG DOWNSIDE.

BRD costs producers between $500 million and $900 million annually.[1] What is it costing your operation?

The risk of BRD comes with every new truckload of calves. Maybe it's time for a change.

1. BRD bacteria are in the upper respiratory tract of even healthy animals.
2. Viral infections or stress from shipping allows bacteria to accumulate in the lungs.
3. Bacteria colonize and proliferate, causing BRD.

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.*

24-HOUR RAPID RESPONSE.

In treatment field trials in clinically ill cattle, ZACTRAN® (gamithromycin)-treated cattle showed a visible improvement in physical appearance within 24 hours.[1]

Of the sick cattle with rectal temperatures above 104 °F, more than 3/4 of ZACTRAN-treated cattle dropped below 104 °F within 24 hours.[3]

THAT OUGHT TO HELP YOU
BREATHE A BIT EASIER.

10-DAY TREATMENT *and* CONTROL.

In the same BRD *treatment* trials, the majority of clinically ill cattle treated with ZACTRAN® (gamithromycin) recovered and stayed healthy for the 10-day study.[1]

On top of that, in BRD *control* field trials, the majority of lightweight, long-haul, high-risk cattle treated with ZACTRAN stayed healthy for the 10-day study.[2]

ENJOY YOUR SIGH OF RELIEF.

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DESIGNED *for* THE WAY YOU USE IT.

- ZACTRAN® (gamithromycin) is administered subcutaneously in the neck at 2 mL/110 lbs.[4]
- Convenient, ready-to-use sterile solution[4]
- Ease of injection at a wide range of temperatures
- In safety studies, other than injection site reactions, no clinically significant adverse drug-related effects were observed[4]
- Available in 100, 250 and 500 mL bottle sizes
- All 250 and 500 mL bottles are enclosed in individual plastic bottle protectors
- Store at or below 77 °F (25 °C) with excursions between 59-86 °F (15-30 °C)
- Use within 18 months of first puncture

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.*

ZACTRAN® (gamithromycin) *is structurally different.*[4,5]

The patented molecule in ZACTRAN, gamithromycin, is a novel subclass of macrolide with a structural difference.[4]

ZACTRAN is rapidly absorbed, rapidly and extensively distributed in lung tissue and persists at high levels in lung tissue for an extended period.[4,5*]

ZACTRAN reaches levels of MIC_{90} within 30 minutes after subcutaneous injection.[6*]

The FIRST NEW MACROLIDE *since 2005.*

**Clinical relevance has not been determined.*

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Dosing for
ZACTRAN® (gamithromycin)

Body Weight (lb.)	2 mL per 110 lbs. Subcutaneous (SC) Dose Volume (mL)
110 lb.	2.0 mL
135 lb.	2.5 mL
165 lb.	3.0 mL
190 lb.	3.5 mL
220 lb.	4.0 mL
245 lb.	4.5 mL
275 lb.	5.0 mL
300 lb.	5.5 mL
330 lb.	6.0 mL
355 lb.	6.5 mL
385 lb.	7.0 mL
410 lb.	7.5 mL
440 lb.	8.0 mL
465 lb.	8.5 mL
495 lb.	9.0 mL
520 lb.	9.5 mL
550 lb.	10.0 mL

Administer up to 10 mL per injection site

Full prescribing information in pocket.

500 mL bottle contains solution for 50 head of 550-lb. cattle.

INDICATIONS[4]

ZACTRAN® (gamithromycin) is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* 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 *M. haemolytica* and *P. multocida*.

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.*

CALCULATE YOUR COST PER HEAD *with* ZACTRAN® (gamithromycin)

Cattle Weight _____ lb.

Bottle Cost $ _____

Bottle Size _____mL

Cost per mL $ _____

Dose Size _____mL*

Cost $ _____ per head

**Syringe set in 1/2 mL increments*

Precise dosing can save you money.

- Each 1/2 cc treats 27.5 lbs. of body weight.
- Allows you to dial in close to actual weight.

CALCULATE YOUR COST PER HEAD *with* YOUR CURRENT PRODUCT

Cattle Weight _____ lb.

Bottle Cost $ _____

Bottle Size _____mL

Cost per mL $ _____

Dose Size _____mL*

Cost $ _____ per head

**Syringe set in 1/2 mL increments*

Every 1/2 cc click of the syringe costs money, so ask about switching to prescription ZACTRAN.

ZACTRAN®
(gamithromycin)

NADA 141-328, Approved by FDA

150 mg/mL ANTIMICROBIAL

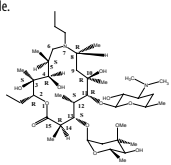
For subcutaneous injection in beef and non-lactating dairy cattle only. Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

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 monothioglycerol 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-dideoy-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* and *Histophilus somni* 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 exceed the MIC_{90} 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 ($T_{½}$) 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 (MIC's) 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)
M. haemolytica	2004	89	1	1	0.5 to >32
P. multocida	2004	79	0.5	1	0.12 to >32
H. somni	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 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 su ccesses 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 Limited
3239 Satellite Blvd., Duluth, GA 30096-4640 U.S.A.
Made in Austria
US. Patent Numbers - 5,985,844, 6,054,434, 5,958,888, 6,239,112

M088812/00 US Code 5719 Rev. 03/2011

DON'T LET BRD GET YOU
or your cattle
DOWN.

500, 250 and 100 mL

ZACTRAN®
(gamithromycin)

Rapid response in 24 hours[1]
10-day treatment and control with a single injection[1,2]
A real alternative for BRD

1 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):171-180.

2 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):189-197.

3 Data on file at Merial.

4 ZACTRAN product label.

5 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.

6 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.

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