Because it’s critical, it’s ZACTRAN™ (gamithromycin)

Rapid response in 24 hours¹
10-day treatment and control¹,²
A real alternative for BRD
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ZACTRAN® (gamithromycin) for bovine respiratory disease (BRD) treatment and control in high-risk cattle

The active ingredient in ZACTRAN, gamithromycin, is rapidly absorbed, rapidly and extensively distributed in lung tissue, and persists at high levels in lung tissue for an extended period.\(^3,4^*\)

ZACTRAN is a novel subclass of macrolide with a structural difference.\(^5\) Administer prescription ZACTRAN subcutaneously (SC) at 2 mL/110 lbs. body weight (6 mg/kg).

\(^*\) Clinical relevance has not been determined.

**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.
Pharmacokinetic and pharmacodynamic characteristics

- ZACTRAN® (gamithromycin) is ≥95% bioavailable following subcutaneous (SC) injection.4
- ZACTRAN is rapidly and extensively distributed throughout the lungs following SC injection.3,5
- ZACTRAN reaches levels above MIC90 for common bacterial BRD pathogens in lung tissue within 30 minutes.5
- ZACTRAN remains at high concentrations above MIC90 in lung tissue and bronchoalveolar lavage (BAL) cells for 10 days.5

* Clinical relevance has not been determined.

Clinical study results

- In field trials, cattle treated with ZACTRAN showed a rapid response and significant improvement in BRD clinical signs within 24 hours after treatment.1
- In field trials, ZACTRAN provided 10-day treatment and control of BRD from a single dose.1,2

Indications3

ZACTRAN is indicated for the treatment of 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 M. haemolytica and P. multocida.

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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 discase 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 10µg/mL (Mueller-Hinton broth) and after exposure for 6 hours 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 MIC90 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 (AUC) observed in lysed ELF cells (e.g., alveolar macrophages) are at least 200-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 (~3.5 days) 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>
<thead>
<tr>
<th>Indicated Pathogens</th>
<th>Years of Isolation</th>
<th>No. of Isolates</th>
<th>MIC**</th>
<th>MIC***</th>
<th>MIC range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. haemolytica</td>
<td>2004</td>
<td>89</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5 to 3.2</td>
</tr>
<tr>
<td>P. multocida</td>
<td>2004</td>
<td>79</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5 to 3.2</td>
</tr>
<tr>
<td>H. somni</td>
<td>2004</td>
<td>32</td>
<td>0.5</td>
<td>0.5</td>
<td>0.25 to 1.0</td>
</tr>
</tbody>
</table>

* 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=0.0021]). 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<0.01 and p<0.001) than the percentage of successes in the cattle treated with saline (36% and 54%).

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.
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Chemistry and mode of action of ZACTTRAN® (gamithromycin)

- ZACTTRAN has a novel structure\(^3\)
- A dibasic macrolide of the 7a-azalide subclass\(^3\)
- Contains two basic nitrogens, including an alkylated nitrogen in the lactone ring\(^4\)
- Lipophilic properties that enhance cellular membrane permeability\(^4-7\)
- Inhibits bacterial protein synthesis\(^5\)
ZACTRAN® is structurally different.3*

ZACTRAN is a novel subclass of macrolide with a structural difference. The patented active ingredient in ZACTRAN, gamithromycin, is rapidly absorbed, extensively distributed in lung tissue and persists at high levels for an extended period.3-5*

ZACTRAN is a novel 15-membered dibasic macrolide from the 7a-azalide subclass. It contains two basic nitrogens, including an alkylated nitrogen in the lactone ring that provides increased basicity, high acid stability and complete bioavailability.3,4* This patented molecule is a different type of macrolide (dibasic/azalide) for the cattle antimicrobial market.3

Gamithromycin was originally synthesized by the Research Laboratories of Merck & Co., Inc. Its potential as an antimicrobial for veterinary medicine was realized through a development program conducted by Merial Pharmaceutical Research & Development.

* Clinical relevance has not been determined.

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Like other macrolides, gamithromycin is able to penetrate the bacterial cell membrane. Once inside the cell, the molecule binds to the 50s ribosome subunit, inhibiting protein synthesis. Gamithromycin inhibits the translocation process between 30s and 50s ribosomes, causing premature detachment of incomplete peptide chains. Unable to produce the proteins it needs to sustain life, the bacterial cell dies.

**Mode of action of ZACTRAN® (gamithromycin)**

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Pharmacokinetics of ZACTRAN® (gamithromycin)

- Rapid, complete absorption\(^3\star\)
- ≥ 95% bioavailability\(^4\star\)
- Low (26%) plasma protein binding\(^3\star\)
- High (74%) available free drug\(^3\star\)
- Above MIC\(_{90}\) in lung tissue within 30 minutes of SC injection\(^5\star\)
- Remains above MIC\(_{90}\) in lung tissue for 10 days\(^5\star\)

* Clinical relevance has not been determined.
Pharmacokinetics of ZACTRAN® (gamithromycin)


The purpose of this study was to examine the pharmacokinetics of gamithromycin, specifically lung and plasma concentrations following SC injection. The study protocols included:

* **Study A)** PK of gamithromycin in live cattle (26 clinically healthy cattle).

* **Study B)** Plasma and lung concentrations, and plasma antibacterial activity of gamithromycin in cattle (36 clinically healthy cattle).

* **Study C)** In vitro binding of gamithromycin to plasma proteins (determined using radiolabelled test substance and ultrafiltration in Heparin-treated plasma).

ZACTRAN is rapidly absorbed and fully bioavailable.\(^3,4^*\)

After SC injection at 6 mg/kg (2 mL/110 lbs.), ZACTRAN is rapidly and completely absorbed, with excellent bioavailability.\(^3,4^*\) The formulation quickly moves into blood plasma, reaching maximum plasma levels (C\(_{\text{max}}\)) within one hour.\(^3^*\) Most important, ZACTRAN moves through blood plasma with low plasma protein binding (26%), allowing rapid and extensive distribution in lung tissue.\(^3,4^*\)

\(^*\) Clinical relevance has not been determined.

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ZACTRAN® (gamithromycin) is present at the site of infection.⁴,⁵*

Gamithromycin moves quickly from blood plasma.⁴,⁵* In the original PK study, ZACTRAN reached maximum peak concentration (Cₘₐₓ) in lung tissue within 24 hours, the first time-point measured.⁴⁸ In the subsequent bronchoalveolar lavage (BAL) study, it was found gamithromycin reached MIC₉₀ for *M. haemolytica* in lung tissue within 30 minutes and reached peak concentration (Cₘₐₓ) in lung tissue within 12 hours.⁵⁸

ZACTRAN remains at high levels in the lungs for an extended period.⁴,⁵*

![Graph showing gamithromycin concentration in lung tissue and plasma over time](image)

In this study, ZACTRAN remained above MIC₉₀ (1 μg/g) for *M. haemolytica, P. multocida* and *H. somni* for 10 days.⁴⁸

* Clinical relevance has not been determined.

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Pharmacodynamics of ZACTRAN® (gamithromycin)

- Rapid, complete absorption\(^3\)
- Above MIC\(_{90}\) in lung tissue within 30 minutes of SC injection\(^5\)
- \(C_{\text{max}}\) in lung tissue within 12 hours\(^5\)
- \(C_{\text{max}}\) in BAL cells and PELF within 24 hours\(^5\)
- Remains above MIC\(_{90}\) in lung tissue for 10 days\(^5\)

* Clinical relevance has not been determined.
Pharmacodynamics of ZACTRAN® (gamithromycin)


The objective of this study was to determine the disposition of ZACTRAN in plasma, pulmonary epithelial lining fluid (PELF), BAL cells and lung tissue homogenate in cattle.

Macrolides preferentially concentrate in lung tissues, such as pulmonary leukocytes, and can reach MIC$_{90}$ levels in these tissues, even when plasma concentrations are well below MIC$_{90}$.\textsuperscript{5a}

Thirty-three healthy Angus calves were randomly allocated to 11 groups of three animals per group. One group served as negative controls. Blood plasma, BAL fluid and lung tissue samples were collected at 0 minutes, 30 minutes, 2, 4, 8 and 12 hours, and at 1, 3, 7, 10 and 15 days from the respective groups.

Because of the unique behavior of the macrolide class, BAL yields more accurate and useful data on the disposition of the drug in important tissues within the lung. Whereas, lung homogenate disrupts cell membranes, making it impossible to distinguish between intracellular and extracellular fluids, BAL allows observation of drug disposition within whole cells in PELF.

The results of this study confirmed the rapid, extensive distribution of gamithromycin to lung tissues, as well as the persistence at high levels for at least 10 days following SC administration.\textsuperscript{5a}

\textsuperscript{*} Clinical relevance has not been determined.

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**Key terms**

**Pharmacodynamics (PD)** — The study of the physiological effects of a drug and the mechanisms of action in a living organism.

**Bronchoalveolar Lavage (BAL)** — Diagnostic procedure where sterile saline is introduced into bronchial and alveolar airspaces of the lung and then aspirated to collect cells and fluids of the airways and lung, collectively referred to as BAL fluid.

**BAL Cells** — The cellular component contained in BAL fluid, primarily cells of the immune system, like leukocytes and macrophages.

**Pulmonary Epithelial Lining Fluid (PELF)** — The fluid that lines the small airways and epithelial surfaces in the lung, the non-cellular component of BAL fluid.

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**ZACTRAN® (gamithromycin) in PELF and BAL cells**

PELF is the primary point of BRD infection. Because *M. haemolytica*, *P. multocida* and *H. somni* are extracellular pathogens, drug concentrations in PELF are considered to be clinically relevant.

BAL cells are primarily infection-fighting immune cells, like leukocytes and macrophages. Gamithromycin concentrates within these cells and can then be actively transported to the site of respiratory infection.

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Macrolides concentrate in the lysosomes and travel with immune cells to the site of lung infection, attacking bacteria as they are engulfed or releasing drug into the PELF.

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* Clinical relevance has not been determined.

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**Results**

Within 30 minutes after SC injection, ZACTRAN reaches lung concentrations above \( \text{MIC}_{90} \) for *M. haemolytica*, *P. multocida* and *H. somni*.\(^5^*\)

Gamithromycin is at peak lung tissue concentration within 12 hours, with peak concentrations in BAL cells and PELF at 24 hours.\(^5^*\)

\(^*\) Clinical relevance has not been determined.

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ZACTRAN® (gamithromycin) remains at high levels for 10 days.5*

Results

After rapidly reaching MIC₉₀ levels, ZACTRAN remains above MIC₉₀ (M. haemolytica, P. multocida and H. somni) for 10 days in lung tissue and BAL cells.5*

* Clinical relevance has not been determined.

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10-day BRD treatment study with ZACTRAN® (gamithromycin)

- Cattle treated with ZACTRAN responded within 24 hours\(^1\)
- Of cattle treated with ZACTRAN with rectal temperatures above 104 °F, over 76% had a significant decrease in temperature within 24 hours\(^11\)
- Cattle treated with ZACTRAN had decreased average depression scores\(^1\)
- Cattle treated with ZACTRAN had decreased average respiratory character scores\(^1\)
- The majority of cattle treated with ZACTRAN stayed healthy for the 10-day study\(^{1,3}\)
10-day BRD treatment study with ZACTRAN® (gamithromycin)


As part of the FDA approval process, four field trials evaluated ZACTRAN as a treatment in feeder cattle displaying clinical signs of BRD. Trials were conducted at four feedyards or research facilities 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. For three days post-arrival, calves displaying clinical signs of BRD (depression score ≥ 1, respiratory character score ≥ 1, rectal temperature ≥ 40 °C/104 °F) were enrolled in the study and received a single 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.¹¹

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. In cattle treated with ZACTRAN, 76.5% with body temperatures over 104 °F experienced a significant decrease in body temperature within 24 hours post-treatment.

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Cattle treated with ZACTRAN® (gamithromycin) had decreased average depression scores.¹

Results

Average depression scores for ZACTRAN-treated cattle decreased from a score of 1.3 to 0.6 within 24 hours post-treatment.¹

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

Cattle treated with ZACTRAN had decreased average respiratory character scores.¹

Results

Average respiratory character scores of ZACTRAN-treated cattle decreased from 1.5 to 0.7 in the first 24 hours post-treatment.¹

Cattle that received ZACTRAN had low average respiratory character scores from Day 1 through Day 10.¹

The majority of cattle treated with ZACTRAN stayed healthy for the 10-day study.¹,³

Results from this BRD treatment study showed clinically ill cattle treated with ZACTRAN had decreased average depression scores, respiratory character scores and rectal temperatures over the 10 days of the study.¹

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ZACTRAN® (gamithromycin) for the treatment of Bovine Respiratory Disease (BRD) including *Mycoplasma bovis*

- ZACTRAN demonstrated efficacy for the treatment of BRD associated with *M. bovis*
Mycoplasma bovis is a member of the class Mollicutes, bacteria that lack a cell wall and instead have a complex plasma membrane. *M. bovis* is an important pathogen of bovine respiratory disease (BRD) in feedyard, stocker and dairy calves. Though BRD often involves more than one pathogen, including *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*, *M. bovis* is often a contributing etiology to bacterial pneumonia or BRD.

ZACTRAN was approved in 2011 for the treatment and control of BRD. This report summarizes research conducted to achieve a post-approval treatment claim for *M. bovis*. The research includes a comprehensive challenge study and field studies conducted in commercial feedyard cattle.

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M. bovis challenge study design.\textsuperscript{12}


Forty colostrum-deprived, cross-bred beef calves three to eight months of age were challenged endobronchially with 60 mL of M. bovis suspension (2.37 x 10\textsuperscript{10} CFU). Thirty-one calves became clinically ill, displaying a depression score ≥1, respiratory character score ≥1 and rectal temperature ≥103.5 °F; 30 were enrolled in the study, 15 per group. One group received a subcutaneous injection of sterile saline (2 mL/110 lbs.), and the second group received ZACTRAN (2 mL/110 lbs.). Clinical assessments were conducted daily from Day -2 through Day 10. On Day 10, lungs were harvested and scored according to the percentage of pneumonic tissue.

Cattle treated with ZACTRAN had decreased average depression and decreased average respiratory character scores.\textsuperscript{12}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{depression_scores.png}
\caption{Mean Depression Scores}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{respiratory_scores.png}
\caption{Mean Respiratory Scores}
\end{figure}

\*Significantly different from control group on days 3-6; \(P \leq 0.05\)

\*Significantly different from control group on days 3-6,8,10; \(P \leq 0.05\)

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
Days after Treatment & 0 & 1 & 3 & 5 & 7 & 9 & 2 & 4 & 6 \\
\hline
Mean Depression Score & 0.0 & 0.2 & 0.4 & 0.6 & 0.8 & 1.0 & 1.2 & 1.4 & 1.6 \\
\hline
Control (Saline) & & & & & & & & & \\
Gamithromycin (6 mg/kg) & & & & & & & & & \\
\hline
\end{tabular}
\caption{Mean Depression Scores}
\end{table}

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Gamithromycin (6 mg/kg) & & & & & & & & & \\
\hline
\end{tabular}
\caption{Mean Respiratory Scores}
\end{table}

\textbf{Results}

On each of the 10 days, ZACTRAN-treated cattle had lower average depression scores and average respiratory character scores than control cattle. There was a statistical difference on days three through six in both scores, additional significant difference was seen on days eight and 10 in respiratory character scores (\(P \leq 0.05\)).

\begin{table}[h]
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\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
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Days after Treatment & 0 & 1 & 3 & 5 & 7 & 9 & 2 & 4 & 6 \\
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Days after Treatment & 0 & 1 & 3 & 5 & 7 & 9 & 2 & 4 & 6 \\
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\hline
Control (Saline) & & & & & & & & & \\
Gamithromycin (6 mg/kg) & & & & & & & & & \\
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\textbf{RESULTS}

On each of the 10 days, ZACTRAN-treated cattle had lower average depression scores and average respiratory character scores than control cattle. There was a statistical difference on days three through six in both scores, additional significant difference was seen on days eight and 10 in respiratory character scores (\(P \leq 0.05\)).

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\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
Days after Treatment & 0 & 1 & 3 & 5 & 7 & 9 & 2 & 4 & 6 \\
\hline
Mean Depression Score & 0.0 & 0.2 & 0.4 & 0.6 & 0.8 & 1.0 & 1.2 & 1.4 & 1.6 \\
\hline
Control (Saline) & & & & & & & & & \\
Gamithromycin (6 mg/kg) & & & & & & & & & \\
\hline
\end{tabular}
\caption{Mean Depression Scores}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
Days after Treatment & 0 & 1 & 3 & 5 & 7 & 9 & 2 & 4 & 6 \\
\hline
Mean Respiratory Score & 0.0 & 0.2 & 0.4 & 0.6 & 0.8 & 1.0 & 1.2 & 1.4 & 1.6 \\
\hline
Control (Saline) & & & & & & & & & \\
Gamithromycin (6 mg/kg) & & & & & & & & & \\
\hline
\end{tabular}
\caption{Mean Respiratory Scores}
\end{table}

\textbf{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 had significantly less lung consolidation\textsuperscript{13}

\begin{center}
\includegraphics[width=0.4\textwidth]{lung_consolidation.png}
\end{center}

\textbf{Lung consolidation results}

Cattle treated with ZACTRAN had a lower average percentage lung consolidation (4.6\%) (pneumonia) than control cattle (14.0\%) \((P=0.024)\).

\textbf{After the challenge study, Merial proceeded to treatment field studies in commercial feedyard cattle.}

\textbf{\textit{M. bovis} field studies\textsuperscript{14}}


In two randomized, negative control, blinded studies, beef and dairy calves between five and 10 months of age were obtained from southeastern sale barns and shipped to two Midwest feedyards. A total of 502 calves were enrolled showing clinical signs of BRD (temperature of ≥104 °F and a depression score or respiratory character score of ≥2). Nasopharyngeal swabs (for laboratory culture of \textit{M. bovis}) were collected on eligible calves prior to receiving subcutaneous ZACTRAN (2 mL/110 lbs.) or sterile saline (2 mL/110 lbs.). Calves were returned to their home pen in replicates. Study calves were scored daily, and on Day 10, treatment success was assessed by a depression score ≤1, a respiratory character score ≤1 and rectal temperature <104 °F.

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Results – Overall treatment success (all BRD etiologies)

At Study Site 1, 74.4% of ZACTRAN-treated cattle were successes on Day 10, versus 24.0% of saline control cattle ($P<0.001$). At Study Site 2, 67.4% of ZACTRAN-treated cattle were successes on Day 10, versus 46.2% of saline control cattle ($P=0.002$).

<table>
<thead>
<tr>
<th>Site</th>
<th>Treatment Group</th>
<th>Treatment Successes n/N</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZACTRAN (gamithromycin)</td>
<td>90/121 (74.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Saline Control</td>
<td>29/121 (24.0%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ZACTRAN (gamithromycin)</td>
<td>87/129 (67.4%)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Saline Control</td>
<td>60/130 (46.2%)</td>
<td></td>
</tr>
</tbody>
</table>

The proportion of calves that were treatment successes were analyzed using the GLIMMIX procedure of SAS® Version 9.1.3. Treatment group was the fixed effect, and pen and pen × treatment interaction were the random effects. Two-sided P-value determined by F-test comparing the expected proportion of successes.

All 502 calves in the studies listed above received a pre-treatment nasopharangeal swab. Each calf was tested by two independent methods for the presence of *Mycoplasma bovis* using industry-standard Microbiological Culture and PCR testing methodologies. All 102 calves reported in the *M. bovis* table below tested positive by culture and by PCR. Any calf that tested negative by either test was excluded from the study results. By setting the high standard to be positive by both culture and PCR, veterinarians can be assured these calves were positive for an active *M. bovis* infection.

Results – *M. bovis* Treatment Success

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total Number of Animals Positive for <em>M. bovis</em></th>
<th>Treatment Success on Day 10**</th>
<th>Treatment Failures on Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZACTRAN (gamithromycin)</td>
<td>63</td>
<td>50 (79.4%)</td>
<td>13 (20.6%)</td>
</tr>
<tr>
<td>Saline Control</td>
<td>39</td>
<td>5 (12.8%)</td>
<td>34 (87.2%)</td>
</tr>
</tbody>
</table>

*An animal was a treatment success for *M. bovis* if it was declared a treatment success on Day 10 and the pre-treatment nasal swab was positive for *M. bovis* on both microbiologic culture and PCR tests. **Number of cattle that were either treatment successes on Day 10 or were not. The percentage this represents of the total for the treatment group is listed in parentheses.

Conclusion: ZACTRAN is effective for treatment of bovine respiratory disease (BRD) associated with *Mycoplasma bovis*.

Based on the results of these studies, ZACTRAN is effective and approved for the treatment of BRD associated with *M. bovis* in beef and non-lactating dairy cattle, in addition to the predominant pathogens, *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.

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10-day BRD control study with ZACTRAN® (gamithromycin)

- ZACTRAN controlled BRD in the majority of lightweight, long-haul, high-risk cattle for the 10-day study\(^2\)
Field trial design


Sale barn calves (68 bulls and 91 steers) were purchased in Kentucky and Tennessee, and transported to Study Site 1 in Nebraska. Investigators 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 control group (saline SC at 2 mL/110 lbs.).

ZACTRAN controlled BRD for the 10-day study in high-risk cattle.²

Significantly (P<0.05) more ZACTRAN-treated cattle remained healthy for the entire 10-day study than saline control cattle.³ Based on the results of these clinical field trials, ZACTRAN demonstrated effectiveness (P<0.05) at controlling BRD in the majority of lightweight, long-haul, high-risk cattle for 10 days after arrival.²
Formulation, dosing, safety and syringability of ZACTRAN® (gamithromycin)

- Ready-to-use sterile solution
- Administer SC in the neck at 2 mL/110 lbs. body weight (6 mg/kg)
- Ease of injection at a wide range of temperatures, with a minimal increase in viscosity at temperatures below freezing$^{15}$
- In safety studies, other than injection site reactions, no clinically significant drug-related effects were observed$^{3}$
Formulation, dosing, target animal safety and syringability of ZACTRAN® (gamithromycin)

Formulation

ZACTRAN is a ready-to-use sterile parenteral solution. Each mL of solution contains 150 mg of gamithromycin as the free base, 1 mg of monothioglycerol and 40 mg of succinic acid in a glycerol formal vehicle.3

Administration and dosing

ZACTRAN has a unique formulation that is administered to cattle SC in the neck at 2 mL/110 lbs. body weight (6 mg/kg).3 It is important to administer ZACTRAN according to the label.

If the total dose exceeds 10 mL, divide the dose so that no more than 10 mL is administered at each injection site.3 Refer to the chart for dosing by weight:

<table>
<thead>
<tr>
<th>Body Weight (lb.)</th>
<th>Dose Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>2</td>
</tr>
<tr>
<td>220</td>
<td>4</td>
</tr>
<tr>
<td>330</td>
<td>6</td>
</tr>
<tr>
<td>440</td>
<td>8</td>
</tr>
<tr>
<td>550</td>
<td>10</td>
</tr>
<tr>
<td>660</td>
<td>12</td>
</tr>
<tr>
<td>770</td>
<td>14</td>
</tr>
<tr>
<td>880</td>
<td>16</td>
</tr>
<tr>
<td>990</td>
<td>18</td>
</tr>
<tr>
<td>1,100</td>
<td>20</td>
</tr>
</tbody>
</table>

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Target animal safety

In a target animal safety study in healthy six-month-old beef cattle, ZACTRAN® (gamithromycin) was administered by SC injection at 6, 18 and 30 mg/kg of body weight (1x, 3x and 5x labeled dose) on Day 0, 5 and 10 (3x 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 of body weight and 30 mg/kg of body weight 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.

Syringability

The viscosity of ZACTRAN allows for ease of injection at a wide range of ambient temperatures. Some increase in viscosity occurs at sub-freezing temperatures; however, the increase is marginal.

<table>
<thead>
<tr>
<th>Viscosity (Centipoise at °F)</th>
<th>77 °F (25 °C)</th>
<th>50 °F (10 °C)</th>
<th>32 °F (0 °C)</th>
<th>14 °F (-10 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZACTRAN</td>
<td>37.83</td>
<td>75.03</td>
<td>118.45</td>
<td>194.40</td>
</tr>
<tr>
<td>DRAXXIN®</td>
<td>10.64</td>
<td>24.18</td>
<td>43.45</td>
<td>73.07</td>
</tr>
<tr>
<td>MICOTIL®</td>
<td>44.92</td>
<td>122.00</td>
<td>177.65</td>
<td>359.95</td>
</tr>
<tr>
<td>NUFLOR®</td>
<td>80.66</td>
<td>198.00</td>
<td>413.45</td>
<td>855.25</td>
</tr>
</tbody>
</table>

Viscosities at varying temperatures

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Packaging and storage for ZACTRAN® (gamithromycin)

- Available in 500, 250 and 100 mL bottle sizes
- All 500 and 250 mL bottles are manufactured with individual 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
Packaging and storage for ZACTRAN® (gamithromycin)

Packaging

ZACTRAN is available in 500, 250 and 100 mL sizes. The 500, 250 and 100 mL bottles contain sufficient solution to treat 50, 25 and 10 head of 550-lb. (250 kg) cattle, respectively. Each 250 and 500 mL bottle is manufactured with an individual plastic bottle protector as pictured above.

Case quantities

ZACTRAN is packaged six bottles per case; 6 x 100 mL, 6 x 250 mL and 6 x 500 mL.

Storage

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

To obtain a Material Safety Data Sheet (MSDS), contact Merial at 1-888-637-4251.
Bottle protectors

All 500 and 250 mL bottles of ZACTRAN® (gamithromycin) are manufactured with a bottle protector.

Anti-roll design (left). Bottom-mounted bottle hanger (right).

- Two-piece construction with locking threads can be opened and closed
- When the two “lock” symbols align, the threads are in the closed position
- Easy-to-handle ergonomic design
- Polypropylene material can be recycled
- Anti-roll designs help to stop rolling on a tabletop
- Bottom design includes a bottle hanger loop in the center
- Drop-testing program for 500 and 250 mL sizes*

* Merial advises customers to always handle the product with care because plastic bottle protectors can fail in high-impact situations.
Summary of
ZACTTRAN® (gamithromycin)
Summary of ZACTRAN® (gamithromycin)

About ZACTRAN:

• Novel subclass of macrolide with a structural difference
• Treated cattle showed a significant improvement in BRD clinical signs within 24 hours
• Provides 10-day BRD treatment duration
• Provides 10-day BRD control duration
• Convenient and ready-to-use
• A real alternative for BRD treatment and control

* Clinical relevance has not been determined.

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References


3 ZACTRAN product label.


6 Data on file at Merial.


10 Data on file at Merial.

11 Data on file at Merial.


13 Data on file at Merial.


15 Data on file at Merial.
"Because it’s critical, it’s ZACTRAN™
(gamithromycin)