KEEP MORE OF YOUR HARD-EARNED PROFITS WITH ZACTRAN® (gamithromycin)

ZACTRAN effectively knocks out pneumonia so nothing prevents your dairy heifers from breeding on time.

ZACTRAN TREATS ALL MAJOR BRD-CAUSING BACTERIA

ZACTRAN is indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, Histophilus somni and Mycoplasma bovis.

WITH ZACTRAN, YOU TYPICALLY SEE IMPROVEMENT WITHIN 24 HOURS*

In a study, cattle treated with ZACTRAN had lower temperatures, were more alert and were breathing easier within 24 hours.

LESS DEPRESSION

LESS LABORED BREATHING

THE CONVENIENCE OF 10 DAYS OF THERAPY FROM A SINGLE INJECTION6

ZACTRAN keeps working for 10 days, reducing the time and labor associated with repulls. With less handling, cattle experience less stress and setback so they can put more energy into gaining weight.

ZACTRAN REACHES THE SITE OF INFECTION IN JUST 30 MINUTES8**

After you administer ZACTRAN, the broad-spectrum antibiotic rapidly reaches the site of infection — the pulmonary epithelial lining fluid (PELF) of the lungs — where it kills bacteria and stops them from replicating.

ZACTRAN 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. Subcutaneous injection may cause a transient local tissue reaction in some cattle that may result in trim loss of edible tissues at slaughter. NOT FOR USE IN HUMANS. KEEP OUT OF REACH OF CHILDREN.

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**Note:** The graphs and tables are not included in this text representation, but they are typically used to visually represent the data and outcomes discussed in the text. The descriptions in the text should be sufficient for understanding the content without the visual aids.
ZACTRAN® (gamithromycin) TARGETS THE SITE OF INFECTION

ZACTRAN travels in cells of the immune system to the site of infection, where it kills bacteria and prevents them from replicating.

EACH DETECTION AND TREATMENT IS KEY TO THE OPTIMAL DEVELOPMENT OF DAIRY HEIFERS

Risk of disease increases as a result of:

- Failure of passive transfer of antibodies in the colostrum
- When colostral antibodies are declining and full immunity is not developed
- Stressors such as adverse weather, weaning, commingling and regrouping, dehorning, dietary changes, bedding changes and poor condition, transportation, and other immune challenges such as non-respiratory diseases

Make ZACTRAN a key part of your BRD management plan. Talk to your veterinarian or Boehringer Ingelheim representative. Visit ZACTRAN.com.

ZACTRAN 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. Subcutaneous injection may cause a transient local tissue reaction in some cattle that may result in trim loss of edible tissues at slaughter. NOT FOR USE IN HUMANS. KEEP OUT OF REACH OF CHILDREN.
ADVERSE REACTIONS
Animals should be appropriately restrained to achieve the proper route of administration. Use sterile equipment. In the under skin of the shoulder (see illustration).

CONTRAINDICATIONS
As with all drugs, the use of ZACTRAN is contraindicated in animals previously known 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 1-888-637-4321.

RESERVE USES:
Do not treat cattle within 15 days of slaughter. Because a discords in milk has not been established, do not use in dairy cattle within 20 months of age or older. A withdrawal period has not been established for the use of ZACTRAN in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS

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

CLINICAL PHARMACOLOGY

The macrolide antimiobacterial as a class are weak bases and as such concentrate in some tissues (such as pulmonary leukocytes). Prolonged exposure of extravascular pulmonary pathogens to macrolides appears to reflect the slow release of drugs from the intravascular reservoir to the site of action, the pulmonary epithelial barrier lining (EEL). In the EEL that is relevant to the successful treatment and control of BRD, gamithromycin is primarily bacteriostatic at therapeutic concentrations. However, in vitro bacteriologic activity has been observed at concentrations of 10 ng/mL (Weller Herren-bratch) and after exposure to the 6-hour and 24-hour plasma samples derived from cattle dosed at 5 mg/kg by gamithromycin. Bacterial Macrolides typically exhibit substantially higher concentrations in the alveolar macrophages and ELF compared to concentrations observed in plasma. Gamithromycin concentrations in the ELF-9 and ELF-10 reflect the concentrations observed in the plasma. Postmortem gamithromycin concentrations in ELF derived (>10x of M. Heus serum) and M. haemolytica and P. multocida were observed in ELF concentrations in the ELF-9 and ELF-10 that are at least 300-times greater than that in the plasma. Although published studies suggest that inflammation can increase the release of drugs from macrophages and neutrophils, these high concentrations in the alveolar macrophages should not be considered indicative of the magnitude or duration of clearance to the pathogen to which this product is administered.

ZACTRAN administered subcutaneously in the neck of cattle as a single dosage of 6 mg/kg BW 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 (^t1/2) of gamithromycin is approximately 4 days. In vitro plasma protein binding studies show that 26% of the gamithromycin binds to plasma proteins, resulting in the 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.

Residue proportionality was established based on AUC over a range of 3 mg/kg BW to 9 mg/kg BW. A single intramuscular administration 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 (M100-A2). Isolates were selected from treatment non-responsive swabs from neonatal calves 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.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Year</th>
<th>N</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. haemolytica</td>
<td>2004</td>
<td>10</td>
<td>5.5</td>
</tr>
<tr>
<td>M. haemolytica</td>
<td>2005</td>
<td>7</td>
<td>5.5</td>
</tr>
<tr>
<td>M. haemolytica</td>
<td>2006</td>
<td>12</td>
<td>5.5</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.

EFFECTIVE:
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 calves 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 to a calvage on Day 6. 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 (59%) was statistically significantly higher (p = 0.01) than the percentage of successes in the cattle treated with saline (16%). The effectiveness of ZACTRAN for the treatment of BRD associated with M. haemolytica was demonstrated independently at two U.S. study sites. A total of 52 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 to a calvage on Day 6. The percentage of successes in cattle treated with ZACTRAN on Day 6 was statistically significantly higher (p = 0.001) than the percentage of successes in the cattle treated with saline (54%). In addition, in the group of calves 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 407 calves administered ZACTRAN at a rate of 6 mg/kg BW in an equivalent volume of sterile saline was administered as a single subcutaneous injection on day 6. At 48 hours post-treatment, the percentage of successes in cattle treated with ZACTRAN was statistically significantly higher (p = 0.002) than the percentage of successes in the cattle treated with saline (50% and 35%).

ANIMAL SAFETY
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 BW, 1, 3, and 5 times the labeled dose (on Day 5, 7, and 10) times the labeled administration frequency. Injection site reactions (neck swelling, attempts to scratch or lick the injection site, and pawing at the ground) were observed in calves in the 18 mg/kg BW and 36 mg/kg BW groups at 10 minutes post-treatment following each injection. Vital 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 59-84°F (15-30°C). Use within 18 months of first puncture.

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

Marketed by Merial 1239 Sandell Blvd, Duluth, GA 30096-4406 U.S.A.

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7 ZACTRAN product label.
10 A small percentage of cattle may have already suffered lung damage and may be too far gone or will require a litle longer to turn around.
11 **Clinical relevance of ZACTRAN has not been established.**