INJECTABLE TREATMENT GUIDELINES
WHEN FEEDING PULMOTIL® (TILMICOSIN)

Pulmotil treatment must be initiated within the first 45 days of the production period
≥ 10% diagnosed* with BRD to start Pulmotil

Pre-Pulmotil therapy:
• No macrolide use
• Non-macrolide — wait at least 3 days before initiating Pulmotil therapy
  – Or exclude treated calves from the Pulmotil group if within 3 days

During Pulmotil therapy:
• No macrolide use
• Treat with a non-macrolide and return to home pen

Post-Pulmotil therapy:
• Treat with either macrolide or non-macrolide injectable**

*Consult your veterinarian to develop a Pulmotil protocol and to document the specific criteria that will be assessed to determine ≥ 10% BRD diagnosis.
**Pulmotil requires a 28-day slaughter withdrawal.

Antibiotic class reference chart†:

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Macrolides</td>
</tr>
<tr>
<td>Draxin®</td>
<td>Tilmicosin injectable solution</td>
</tr>
<tr>
<td>Micotil®</td>
<td>Tilmicosin injection</td>
</tr>
<tr>
<td>Tylan® injection</td>
<td>Tylosin injection</td>
</tr>
<tr>
<td>Zactran®</td>
<td>Gamithromycin</td>
</tr>
<tr>
<td>Zuprevo®</td>
<td>Tildipirosin injection</td>
</tr>
<tr>
<td></td>
<td>Non-macrolides</td>
</tr>
<tr>
<td>Advocin™</td>
<td>Danofloxacin injection</td>
</tr>
<tr>
<td>Baytril® 100</td>
<td>Enrofloxacin injectable solution</td>
</tr>
<tr>
<td>Bio-Mycin® 200</td>
<td>Oxytetracycline</td>
</tr>
<tr>
<td>Excede®</td>
<td>Ceftiofur crystalline free acid</td>
</tr>
<tr>
<td>Excenel® RTU</td>
<td>Ceftiofur hydrochloride sterile suspension</td>
</tr>
<tr>
<td>Liquamycin® LA-200®</td>
<td>Oxytetracycline injectable solution</td>
</tr>
<tr>
<td>Naxcel®</td>
<td>Ceftiofur sodium sterile powder</td>
</tr>
<tr>
<td>Nuflox®</td>
<td>Florfenicol injectable solution</td>
</tr>
<tr>
<td>Nuflox Gold™</td>
<td>Florfenicol injectable solution</td>
</tr>
<tr>
<td>Restflor Gold®</td>
<td>Florfenicol and Flunixin meglumine</td>
</tr>
<tr>
<td>Tetradure™ 300</td>
<td>Oxytetracycline</td>
</tr>
</tbody>
</table>

†Work with your veterinarian to determine the correct antibiotic(s) for your operation.

Intravenous administration of Pulmotil is contraindicated in calves. Consult your veterinarian for use of Pulmotil to treat calves.

Pulmotil
For the control of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida and Histophilus somni in groups of beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group: Feed continuously for a single, 14-day period at 568 to 757 g/ton of tilmicosin (100% DM basis) in a Type C medicated feed as the sole ration to provide 12.5 mg/kg of body weight/day.

Important Safety Information:
• CAUTION: Federal law restricts medicated feed containing this veterinary feed directive (VFD) drug to use by or on the order of a licensed veterinarian.
• Cattle intended for human consumption must not be slaughtered within 28 days of the last treatment.
• To assure both food safety and responsible use, treatment must be initiated within the first 45 days of the production period. The treatment should not occur concurrent with or following administration of an injectable macrolide, or within 3 days following administration of a non-macrolide injectable BRD therapy.
• VFD expiration date must not exceed 45 days from the time of issuance. VFDs shall not be refilled.
• Use only in cattle fed in confinement for slaughter.
• Cattle with severe clinical illness should be evaluated for individual treatment with an alternative non-macrolide therapy.
• Do not use in female dairy cattle 20 months of age or older or in veal calves.
• Safety has not been established for cattle intended for breeding.
• Do not allow horses or other equines access to feeds containing tilmicosin.

Tylan Injection
Indication: For use in the treatment of bovine respiratory complex (shipping fever, pneumonia) usually associated with Pasteurella multocida and Arcanobacterium pyogenes, foot rot (necrotic pododermatitis) and calf diphtheria caused by Fusobacterium necrophorum and metritis caused by Arcanobacterium pyogenes Directions for use: Inject intramuscularly 8 mg/lb one time daily. Treatment should be continued 24 hours following remission of disease signs, not to exceed 5 days. Do not inject more than 10 mL per site.

Important Safety Information:
• Not for human use. Keep out of reach of children.
• Cattle intended for human consumption must not be slaughtered within 21 days of the last use of this drug product.
• Do not use in dairy cattle 20 months of age or older, including dry dairy cows or in calves intended to be processed for veal.
• Do not administer to horses or other equines. Injection of tylosin in equines has been fatal.
Micotil® 300 Injection

Tilmicosin Injection, USP

Cautions: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description: Micotil® is a solution of the antibiotic, tilmicosin, each ml contains 300 mg of Tilmicosin, USP as tilmicosin phosphate in 35% propylene glycol, phosphoric acid and as needed to adjust pH and water for injection. Q.S. Tilmicosin, USP is produced from a strain of Streptomyces tendae and is the 9, 10-epimer of tilmicosin. It is a white or slightly yellow, crystalline powder with a characteristic odor. It is freely soluble in water. Micotil® is indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni, and for the treatment of respiratory disease in cattle at high risk of developing BRD associated with Mannheimia haemolytica.

Indications: Micotil® is indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni, and for the treatment of respiratory disease in cattle at high risk of developing BRD associated with Mannheimia haemolytica.

Dosage and Administration: Inject subcutaneously in Cattle and Sheep Only. In cattle, administer a single subcutaneous dose of 10 mg/kg body weight (10 ml/kg for a 350 kg cow). In sheep, administer 10 ml of Micotil®/100 lbs body weight. Do not use in animals other than cattle or sheep. Injection of this antibiotic has been shown to be fatal in swine and non-human primates, and it may be fatal in horses and goats.

For all products:
The label contains complete use information, including cautions and warnings. Always read, understand and follow the label and use directions.

**Micotil** is approved for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*, and for the treatment of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*.

Important Micotil Safety Information

Before using this product, it is important to read the entire product insert, including the boxed human warning.

• Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
• Not for human use. Injection of this drug in humans has been associated with fatalities. Keep out of reach of children. Do not use in automated powered syringes. Exercise extreme caution to avoid accidental self-injection. In case of human injection, consult a physician immediately and apply ice or cold pack to injection site while avoiding direct contact with the skin. Emergency medical telephone numbers are 1-800-872-9947 or 1-800-428-4441. Avoid contact with eyes.

• Note To The Physician: The cardiovascular system is the target of toxicity and should be monitored closely. Cardiac arrhythmias may occur due to calcium channel blockade. In dogs, administration of intravenous calcium offset Micotil®-induced tachycardia and negative inotropy (decreased contractility).

• Do not use in lambs less than 15 kg body weight.
• Do not use in female dairy cattle 20 months of age or older. Use in lactating dairy cattle or sheep may cause milk residues.
• Do not use in animals less than 12 months of age or older. Use of tilmicosin in this class of cattle may cause milk residues. Not for use in lactating ewes producing milk for human consumption.

Residue Warnings: Animals intended for human consumption must not be slaughtered within 42 days of the last treatment. Use in lactating dairy cattle 30 months of age or older. Use of tilmicosin in this class of cattle may cause milk residues. Not for use in lactating ewes producing milk for human consumption.

3 Adverse Reactions: The following adverse reactions have been reported post-approval: In cattle: injection site swelling and inflammation, lameness, collapse, anaphylaxis/anaphylactoid reactions, decreased food and water consumption, and death; in sheep: dyspnea and death.

For a complete listing of adverse reactions for tilmicosin phosphate reported to the CVM see http://www.fda.gov/AnimalVeterinary/SafetyHealth/DrugSafetyInformation/s05394.htm

Clinical Pharmacology: A single subcutaneous injection of Micotil® at 10 mg/kg of body weight in cattle resulted in peak plasma concentrations of 0.6 mg/l at 1 hour. However, peak concentrations of tilmicosin remained above the tilmicosin MIC 95% of 0.12 mg/l for *Mannheimia haemolytica* for at least 3 days following the single injection. Serum tilmicosin levels are a poor indicator of total body tilmicosin. The tilmicosin MIC 95% of 0.12 mg/l in favor of tilmicosin for 3 days post-injection at approximately 60.

In a study with radiolabeled tilmicosin, 24% and 68% of the dose was recovered from urine and feces respectively over 21 days. After a single subcutaneous injection of Micotil® at 10 mg/kg of body weight, tilmicosin concentrations in excess of 4 mg/l were maintained in the alveolar macrophages and neutrophils of most cattle for at least 10 days. The clinical relevance of these findings has not been determined.

For a complete list of adverse reactions for tilmicosin phosphate reported to the CVM see http://www.fda.gov/AnimalVeterinary/SafetyHealth/DrugSafetyInformation/s05394.htm

Effective: In a multi-location field study, 1500 calves with naturally occurring BRD were treated with Micotil®. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal appetite, normal activity, normal rectal temperature of ≤104°F on Day 1 or Day 3. The cure rate was significantly higher (P<0.001) in Micotil® treated calves (63.1%) compared to saline-treated calves (29.2%). During the treatment phase of the study, the cure rate was 89.4% for calves treated with Micotil®. Calves which failed to respond to treatment with saline were treated with Micotil®. Kahn, and Pasteurella multocida were associated with the non-responders. Lameness associated with the injection site was noted in two of ten animals (one animal in the 30 mg/kg body weight treatment group and one animal in the 60 mg/kg treatment group). No other drug related lesions were observed macroscopically or microscopically. Decreases in food and water consumption were noted in all treatment groups compared to the control group.

A separate safety study conducted in feeder calves, subcutaneous doses of 10, 20, 30, or 50 mg/kg body weight, injected 3 times at 7-day interval intervals, death was not seen in any of the treatment groups. Response to treatment was compared to saline-treated controls. A cure was defined as a calf with normal appetite, normal activity, normal rectal temperature of ≤104°F on Day 1 or Day 3. The cure rate was significantly higher (P<0.001) in Micotil® treated calves (63.1%) compared to saline-treated calves (29.2%). During the treatment phase of the study, the cure rate was 89.4% for calves treated with Micotil®. Calves which failed to respond to treatment with saline were treated with Micotil®. Kahn, and Pasteurella multocida were associated with the non-responders. Lameness associated with the injection site was noted in two of ten animals (one animal in the 30 mg/kg body weight treatment group and one animal in the 60 mg/kg treatment group). No other drug related lesions were observed macroscopically or microscopically. Decreases in food and water consumption were noted in all treatment groups compared to the control group.

In a separate safety study conducted in feeder calves, subcutaneous doses of 10 mg/kg body weight injected at 72-hour intervals resulted in death at one of the four treated animals. Deaths at the site of injection was noted in all cases. Calves which failed to respond to treatment with saline were treated with Micotil®. Kahn, and Pasteurella multocida were associated with the non-responders. Lameness associated with the injection site was noted in two of ten animals (one animal in the 30 mg/kg body weight treatment group and one animal in the 60 mg/kg treatment group). No other drug related lesions were observed macroscopically or microscopically. Decreases in food and water consumption were noted in all treatment groups compared to the control group.

**Micotil** has a pre-slaughter withdrawal time of 42 days.

Droxin®, Naxcel®, Excenel®, Liquamycin LA-200, Advocin and Excede are the property of Zoetis Inc., its affiliates and/or its licensors.

Baytril is a registered trademark of Bayer.

Nulcor®, Nulcor Gold, Renu Natural, and Nulcor are property of Intervet Inc., a subsidiary of Merck & Co., Inc., its subsidiaries or related companies.

Zactran and Tetradure are registered trademarks of Merial.

Bio-Mycin is a registered trademark of Boehringer Ingelheim Vetmedica, Inc.

Elanco®, Micotil®, Pulmotil®, Tylan® and the diagonal bar are all trademarks owned or licensed by Eli Lilly and Company, its subsidiaries or affiliates.

© 2016 Eli Lilly and Company, its subsidiaries or affiliates.