FULL VALUE BEEF™

How to Prepare for the Veterinary Feed Directive (VFD)

Montana Nutrition Conference and Livestock Forum April 28-29, 2015

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Beef Business Unit

Elanco

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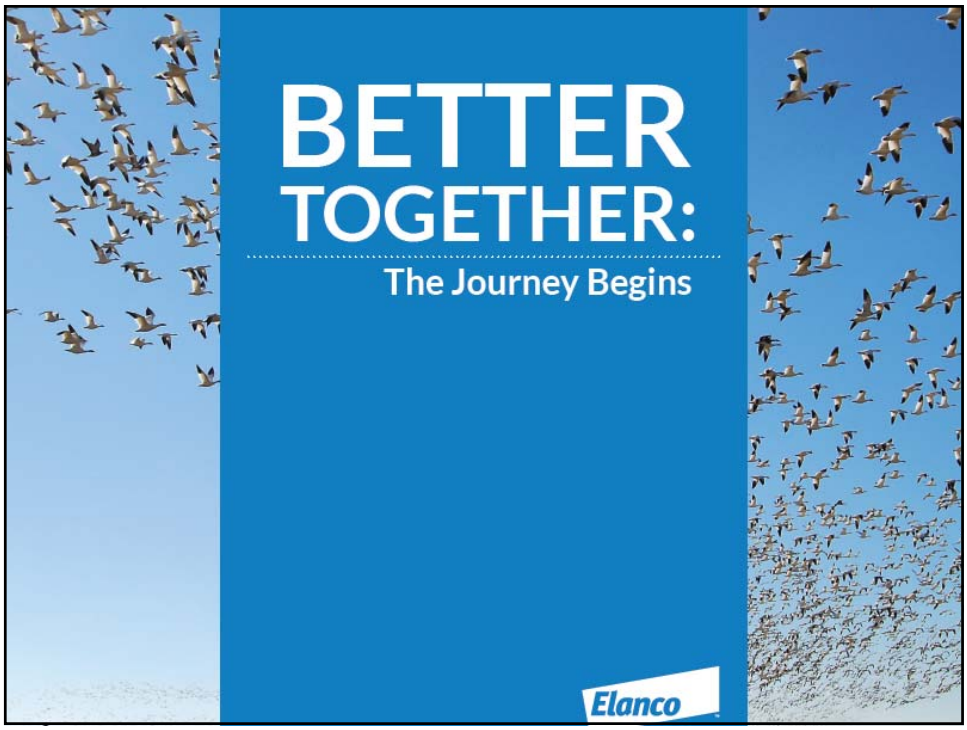

A Robust Portfolio

Health Management Products

Vaccines

ARSENAL® 4.1
BOVINE ECOLIZER®+C20
Bovine Pili Shield®
BRD SHIELD
BVD Shield® 3
Clostridium Perfringens Type A Toxoid
Clostratox®
Clostri Shield®
Fusogard®
Master Guard
NUPLURA PH
PINKEYE SHIELD® XT4
Quick Shield®
ReproSTAR®
SCOUR BOS
Somnu Shield®
Titanium
Vib Shield® Plus L5
VIRA SHIELD

Antibiotics & Parasiticides

Micotil
Pulmotil
StandGuard

Feed Optimization Products

HeifermaX 500
Rumensin
Tylan

End-point Management Products

Component with Tylan
Compudose
Encore
Optaflexx

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Micotil® (tilmicosin injection) is approved for the treatment and control of BRD.

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The Good News

- Today, antibiotics used in farm animals are not top-of-mind
- Few think about them as they shop for food

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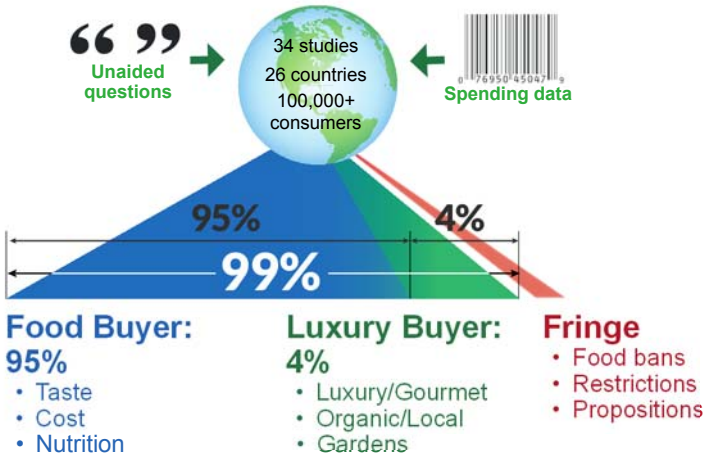
2013 International Consumer Attitudes Study (ICAS)

2nd Edition: May 2013



Consumer Concerns

Antibiotic use, among other things, makes consumers uncomfortable.

1-10 scale; percent responding "uncomfortable" (1-3)	Total	Food communicators	"I'm not aware of this method"
Supplementing naturally occurring animal hormones	55%	72%	2%
Using dihydrogen monoxidization (H_2O) on crops & farm animals	52%	53%	14%
Using pesticides on crops	49%	59%	1%
Administering animal antibiotics	48%	61%	1%
Using genetically modified (GMOs) or biotech seeds	43%	51%	2%
Using fertilizers on crops	26%	31%	—

 Source: ml&p research for USFRA, 10/11, n=1,400

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USBBUMUL00865 Source: ml&p research for USFRA, 10/11, n=1,400

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The Challenge…

It's not what you say, it's what they hear.

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The Disconnect

YOU SAY	THEY HEAR
We use antibiotics to be more efficient.	Because you only care about making money…
We use antibiotics to keep animals healthy.	You HAVE to use antibiotics because animals are kept in poor conditions.
Regulatory agency reviews have approved antibiotics as safe after rigorous review processes.	We don't know if it's safe for the long term. They've been wrong before…
There are rules that dictate maximum residue levels allowed in animals.	How can we be sure ANY residue is safe?
There is no evidence that use of antibiotics in animals causes resistance in humans.	Yeah right. We're using so many, that has to be part of the reason.

What Do We Do?

- In a world where our audience doesn't **TRUST**
  - That antibiotics are safe
  - That they're used judiciously
  - That they're used for the right reasons

Rebuilding Trust in Antibiotics

- Acknowledge concerns
- Accept responsibility
- Add context
- Align language

Access to Antibiotics

- A public health issue
- Access to effective antibiotics

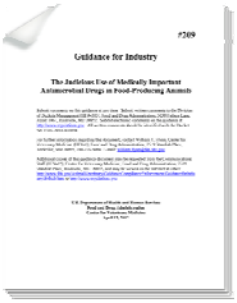
Critical for public health

Vital for livestock & poultry production

Essential for animal well-being

FDA Releases Antibiotic Guidance

- FDA goal: protect human health & curb development of antimicrobial resistance
- 3 proposed documents to modify use of medically-important antibiotics in food producing animals



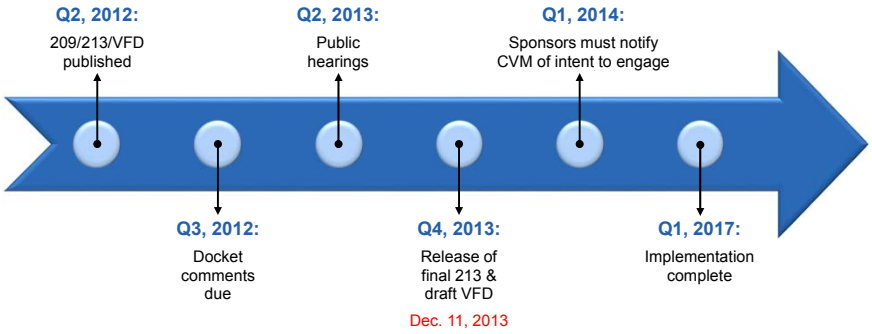
Guidance for Industry (GFI) #209

Guidance for Industry (GFI) #213

CFR 558

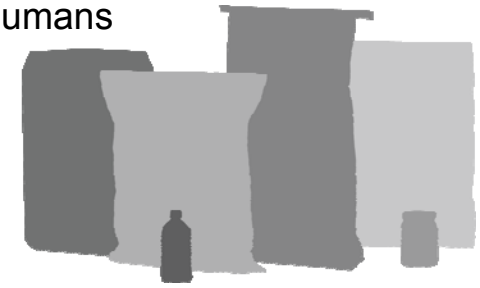
Compliance Timeline

- FDA pursuing voluntary compliance
- FDA to evaluate progress 3 years after final publication
  - Guidance for Industry #213 finalized Dec. 2013
  - FDA will consider "further actions" as warranted



Implications

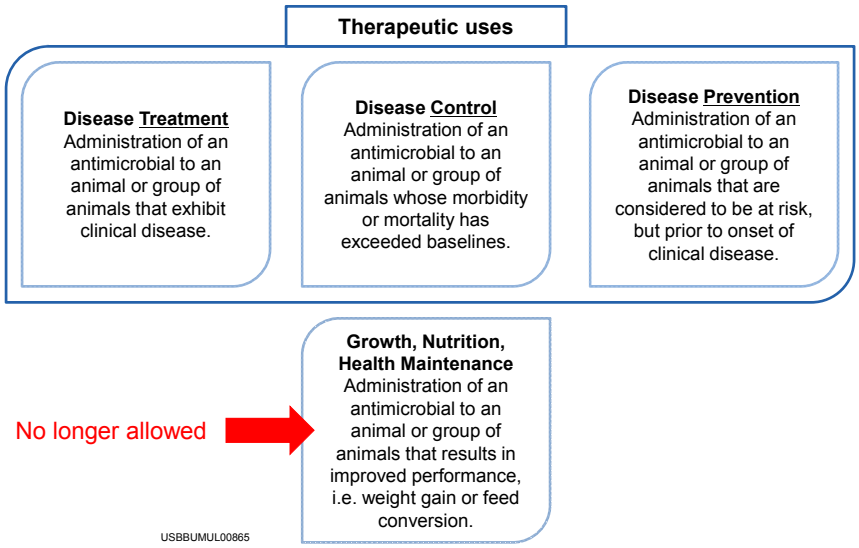
- Food producers aren't losing all feed-grade antibiotics
- The way they're used will change
- Key phrase is "medically-important"
  - Refers to drugs important for therapeutic use in humans



Three Classes of Antibiotics

- **Human-only antibiotics** are not approved for use in animals, creating a reserve of unique antibiotics for human health needs
- Because animals are susceptible to different diseases & have different needs than humans, **animal-only antibiotics** have been developed to treat specific health requirements of animals & are not used in human medicine
- **Shared-class antibiotics** are approved for animals & humans. Going forward, Elanco will only promote this class of antibiotics for therapeutic uses in animals under veterinarian supervision

FDA/CVM (GFI #209) Will Phase Out Performance Indications for Certain Antibiotics



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What Will Change?

Antibiotic classes	Animal-only	Shared-use
Performance	Ionophore — ADG/FE Bambermycin — ADG	CTC — ADG/FE
Prevention	Ionophore — Coccidosis	Oxytetracycline — SFC
Control	Ionophore — Coccidosis Carbodox — dysentery	Tylan — Liver abscess CTC — Pneumonia CTC — Liver abscess CTC — Anaplasmosis
Treatment	Tiamulin — dysentery	CTC — Enteritis

= No longer allowed
= VFD required

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Establishment of VFDs

- First passed in 1996 (ADAA; 21 CFR 558)
- Requires a coordinated effort: producer, veterinarian, nutritionist & feed supplier
  - Requires veterinary oversight of feed use antimicrobials
    - **Written statement (VFD form)** by licensed veterinarian that authorizes client/producer to obtain & use (on designated products)
  - Follow "Standards of Practice" in state where cattle reside. Drops the requirement for VCPR

Modernizing VFD

- GFI #209 proposed to modernize & add "shared-class" products
- *This raised concerns….*
  - Limited experience with VFD process
  - Logistical & administrative burden
  - Access to veterinarians
  - Increased cost (producer, vet, feedmills)

Veterinarian Use & Oversight

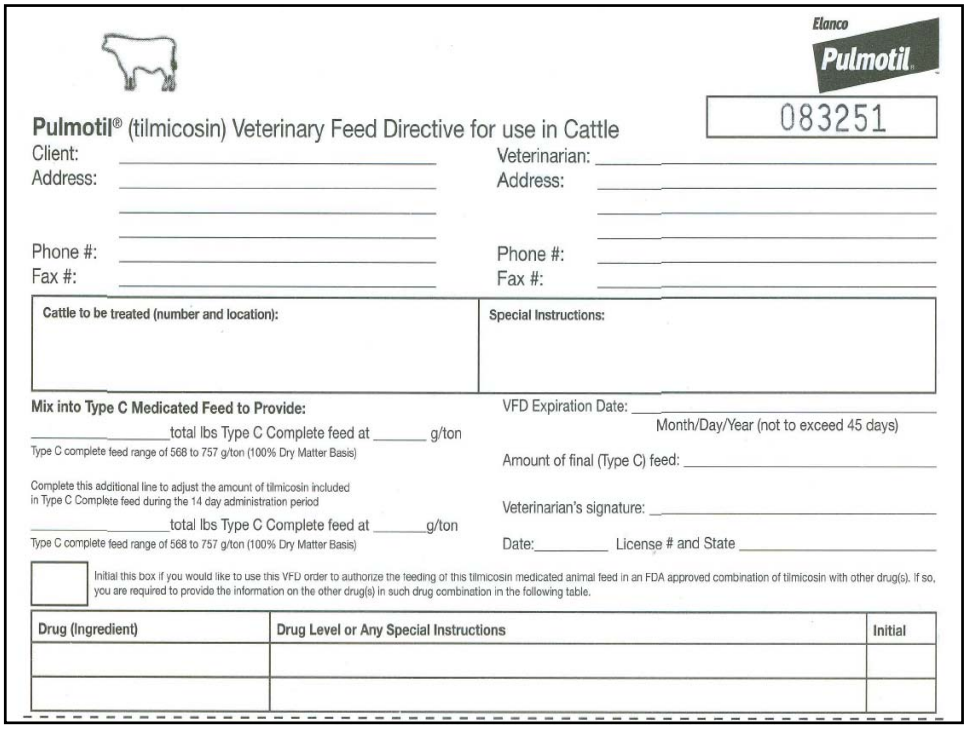
- Each product approved under the VFD regulations includes the following caution:

CAUTION: Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice.

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

VFD Regulations on Distribution

- One-time Notifications
  - Notice to FDA of distribution of VFD feeds
    - Notification to FDA that you intend to handle/distribute VFD drug-containing medicated feeds
  - Acknowledgement of distribution limitations for VFD feeds
    - Document stating that the purchasers will sell the VFD feeds only to producers with valid VFD orders or to other distributors for whom they have acknowledgement notices



Elanco Pulmotil

083251

Pulmotil® (tilmicosin) Veterinary Feed Directive for use in Cattle

Client: _____ Veterinarian: _____

Address: _____ Address: _____

_____ _____

_____ _____

Phone #: _____ Phone #: _____

Fax #: _____ Fax #: _____

Cattle to be treated (number and location):	Special Instructions:

Mix into Type C Medicated Feed to Provide:

_____total lbs Type C Complete feed at _____ g/ton

Type C complete feed range of 568 to 757 g/ton (100% Dry Matter Basis)

Complete this additional line to adjust the amount of tilmicosin included in Type C Complete feed during the 14 day administration period

_____total lbs Type C Complete feed at _____g/ton

Type C complete feed range of 568 to 757 g/ton (100% Dry Matter Basis)

VFD Expiration Date: _____

Month/Day/Year (not to exceed 45 days)

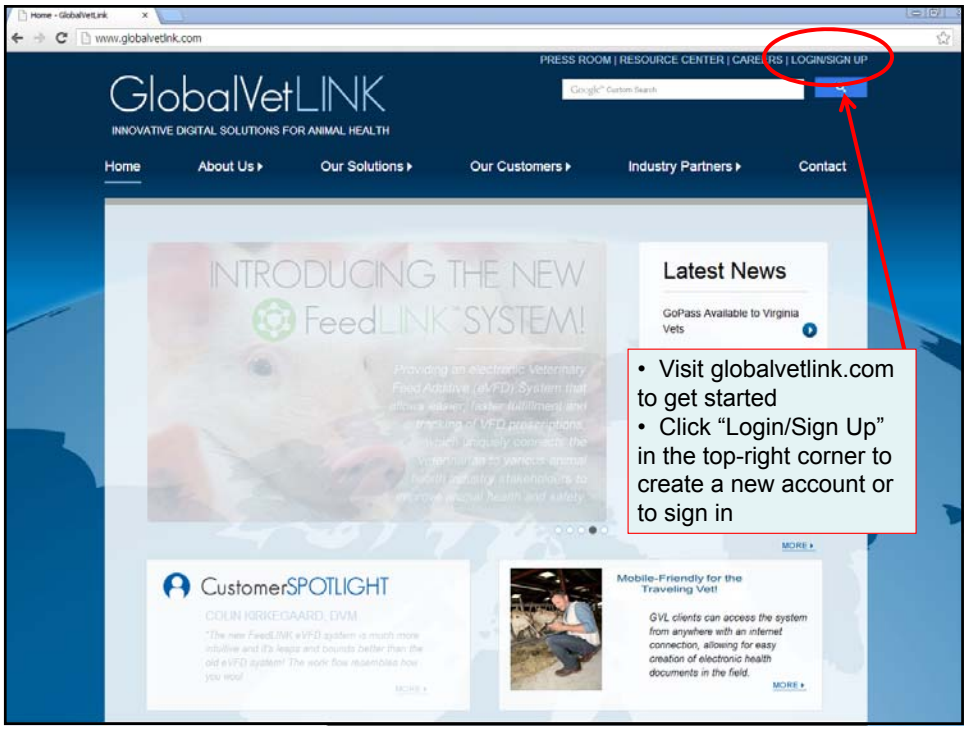
Amount of final (Type C) feed: _____

Veterinarian's signature: _____

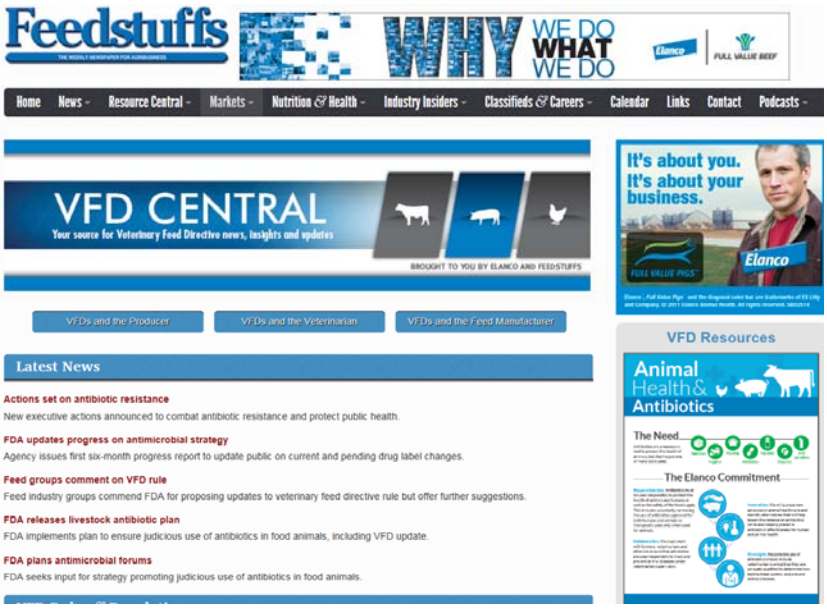
Date:_____ License # and State _____

☐ Initial this box if you would like to use this VFD order to authorize the feeding of this tilmicosin medicated animal feed in an FDA approved combination of tilmicosin with other drug(s). If so, you are required to provide the information on the other drug(s) in such drug combination in the following table.

Drug (Ingredient)	Drug Level or Any Special Instructions	Initial



feedstuffs.com/vfd

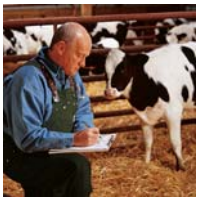


Key Points: Feed Antibiotics & VFD

- Coordinated effort, but still allow judicious use of medically-important antibiotics
  - One-time notification
  - Require vet oversight
  - Pen or group animal detail
  - Written or electronic form authorization
- Effort to protect human & animal health & secure food safety

Investing in Innovation

Pursue advances & treatments that lessen reliance on antibiotics



Seek new therapeutic indications for treatment, control & prevention of diseases

Support use of antimicrobials used only in animals for growth & performance (where permitted)

Provide services that help verify & validate responsible product use

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Thank You

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How to use Tylan®* premix for swine	
For ileitis control:	**Recommendation:**
Feed Tylan at 100 g/ton for at least 3 weeks, followed by 40 g/ton to market weight.	Begin feeding Tylan at 12-15 weeks of age or 3 weeks prior to seroconversion,[1,2] because gross or microscopic lesions appear well in advance of seroconversion/disease.

*** No withdrawal required when fed according to label directions.**

How to use Tylan Soluble for swine
Swine: For the treatment and control of swine dysentery, medicate with 250 mg tylosin per gallon in drinking water for 3 to 10 days, depending upon severity of infection. Alternatively, medicate with 250 mg tylosin per gallon in drinking water for 3 to 10 days, followed by 40 to 100 g tylosin per ton of complete feed (Type C medicated feed manufactured from TYLAN Type A medicated article) for 2 to 6 weeks. For control of porcine proliferative enteropathies (PPE, ileitis), medicate with 250 mg tylosin per gallon in drinking water for 3 to 10 days, followed by 40 to 100 g tylosin per ton of complete feed (Type C medicated feed manufactured from TYLAN Type A medicated article) for 2 to 6 weeks. Swine must consume enough medicated water to provide a therapeutic dose. Only medicated water (250 mg tylosin per gallon) should be available while medicating with TYLAN Soluble.
RESIDUE WARNING: Swine must not be slaughtered for food within 48 hours after treatment.

1. Guedes, R. 2004. "Update on epidemiology and diagnosis of porcine proliferative enteropathy." J. Swine Health Prod. 12(3): 134-138.
2. Armbruster, G., et al. 2007. "Review of *Lawsonia intracellularis* seroprevalence screening in the United States, June 2003 to July 2006." AASV Proc.: 231-233.

How to use Tylan® premix for broilers and breeders

- For increased rate of weight gain feed Tylan at:
  - Tylan 40 per ton of Type C feed: 0.1 to 1.25 lbs.
  - Tylosin per ton of Type C feed: 4 to 50 g
- To aid in the control of chronic respiratory disease associated with *Mycoplasma gallisepticum:*
  - Tylan 40 per ton of Type C feed: 20 to 25 lbs.
  - Tylosin per ton of Type C feed: 800 to 1,000 g
- Feed continuously as the sole ration.
- Tylan requires a 5-day withdrawal period before slaughter when fed at 800-1,000 g/ton.

How to use Tylan Soluble for broilers

- As an aid in the treatment of chronic respiratory disease (CRD) caused by *Mycoplasma gallisepticum* sensitive to tylosin in broiler and replacement chickens. For the control of chronic respiratory disease (CRD) caused by *Mycoplasma gallisepticum* sensitive to tylosin at time of vaccination or other stress in chickens. For the control of chronic respiratory disease (CRD) caused by *Mycoplasma synoviae* sensitive to tylosin in broiler chickens.
- Chickens should be treated for 3 days; however, treatment may be administered for 1 to 5 days depending upon severity of infection. Treated chickens must consume enough medicated water to provide 50 mg/lb. of body weight per day. Only medicated water should be available to the birds.

How to use Tylan Soluble for turkeys

- For maintaining weight gain and feed efficiency in the presence of infectious sinusitis caused by *Mycoplasma gallisepticum* sensitive to tylosin.
- Turkeys should be treated for 3 days; however, treatment may be administered for 2 to 5 days depending upon the severity of infection. Treated turkeys must consume enough medicated water to provide 60 mg/lb. of body weight per day. Only medicated water should be available to the birds.

How to use Tylan® Premix for beef cattle

- For reduction of incidence of liver abscesses associated with *Fusobacterium necrophorum* and *Arcanobacterium pyogenes*:
  - Feed tylosin continuously at 8-10 g/ton (90% DM) to deliver 60-90 mg/hd/d.

Hygromix® directions for use

- For use as an aid in the control of parasite infections in chickens associated with *Ascaris galli*, *Heterakis gallinae* and *Capillaria obsignata*.
- Mix 1.0-1.5 lbs. Hygromix 8 per ton of Type C medicated feed for 8-12 g of hygromycin B per ton.
- Feeds containing Hygromix must be withdrawn 3 days prior to slaughter.

Recommendation[1,2]

Feed to pullets and breeders at 12 g/ton from placement through 50 weeks.

The labels contain complete use information, including cautions and warnings.
Always read, understand and follow the label and use directions.

1. Eckman, M. 1998. "Controlling Helminth Parasites in Layer, Broiler Breeder Flocks." Poultry Sci. June/July.
2. Shumard, R., et al. "Hygromycin B: An Anthelmintic for Effective Control of Nematode Parasites of Chickens." Symposium of Tylan and Hygromix.

Coban® for broilers and breeders

- For coccidiosis prevention, feed Coban at 90-110 g/ton.
- Feed continuously as the sole ration.
- Requires a zero-day withdrawal (when fed according to the label).

CAUTION: Ingestion of monensin by horses and guinea fowl has been fatal.

Coban® for turkeys

- For coccidiosis prevention, feed Coban at 54-90 g/ton.
- Feed continuously as the sole ration.
- Requires a zero-day withdrawal (when fed according to the label).

CAUTION: Ingestion of monensin by horses and guinea fowl has been fatal.

Skycis® indications	Appropriate concentrations of narasin in Type C Medicated Feed
Increased rate of weight gain in growing-finishing swine when fed for at least 4 weeks.	13.6 to 27.2 g/ton (15 ppm to 30 ppm)
Increased rate of weight gain and improved feed efficiency in growing-finishing swine when fed for at least 4 weeks.	18.1 to 27.2 g/ton (20 ppm to 30 ppm)
No increased benefit in rate of weight gain has been shown when narasin concentrations in the diet are greater than 13.6 g/ton (15 ppm).	
No withdrawal period is required when used according to the label.	

Cautions:

– Swine being fed with Skycis (narasin) should not have access to feeds containing pleuromutilins (e.g., tiamulin) as adverse reactions may occur. If signs of toxicity occur, discontinue use.

– Do not allow adult turkeys, horses or other equines access to narasin formulations. Ingestion of narasin by these species has been fatal. Not approved for use in breeding animals because safety and effectiveness have not been evaluated in these animals.

Maxiban® directions for use

- For coccidiosis prevention, feed Maxiban at 54-90 g/ton.
- Feed continuously as the sole ration.
- Requires a 5-day withdrawal.

CAUTION: Ingestion of narasin by adult turkeys, horses or other equine species has been fatal. Do not feed to laying hens.

Monteban® directions for use

- For coccidiosis prevention, feed Monteban at 54-90 g/ton.
- Feed continuously as the sole ration.
- Requires a zero-day withdrawal (when fed according to label).

CAUTION: Ingestion of narasin by adult turkeys, horses or other equine species has been fatal. Do not feed to laying hens.

Rumensin® directions for use

Consumption by unapproved species or feeding undiluted may be toxic or fatal. Do not feed to veal calves.

Dairy Cow: For increased milk production efficiency (production of marketable solids-corrected milk per unit of feed intake):
Total Mixed Rations: Feed continuously to dry and lactating dairy cows a total mixed ration ("complete feed") containing 11 to 22 g/ton monensin on a 100% dry matter basis.
Component Feeding Systems (including top dress): Feed continuously to dry and lactating dairy cows a Type C Medicated Feed containing 11 to 400 g/ton monensin. The Type C Medicated Feed must be fed in a minimum of 1 pound of feed per cow per day to provide 185 to 660 mg/head/day monensin to lactating cows or 115 to 410 mg/head/day monensin to dry cows. This provides cows with similar amounts of monensin they would receive by consuming total mixed rations containing 11 to 22 g/ton monensin on a 100% dry matter basis.
Growing cattle on pasture or in dry lot (Dairy replacement heifers): For increased rate of weight gain: Feed at the rate of not less than 50 nor more than 200 mg/head/day in not less than 1 pound of Type C Medicated Feed; or after the 5th day, feed at the rate of 400 mg/head/day every other day in not less than 2 pounds of Type C Medicated Feed. The monensin concentration in the Type C Medicated Feed must be between 25 and 400 g/ton. During the first 5 days, cattle should receive no more than 100 mg/day contained in not less than 1 pound of feed. Do not self feed.
For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*: Feed at a rate to provide 0.14 to 0.42 mg per pound body weight per day, depending upon severity of challenge, up to a maximum of 200 mg/head/day. The monensin concentration in Type C Medicated Feed must be between 25 and 400 g/ton. During the first 5 days, cattle should receive no more than 100 mg/day contained in not less than 1 pound of feed.

Important Safety Information

- **See label on slide 63 for complete use information, including boxed human warnings and non-target species safety information.**
- Micotil is to be used by, or on the order of, a licensed veterinarian. For cattle or sheep, inject subcutaneously. Intravenous use in cattle or sheep will be fatal. Do not use in female dairy cattle 20 months of age or older. Use in lactating dairy cattle or sheep may cause milk residues.
- The following adverse reactions have been reported: in cattle: injection site swelling and inflammation, lameness, collapse, anaphylaxis/anaphylactoid reactions, decreased food and water consumption, and death; in sheep: dyspnea and death.
- Always use proper drug handling procedures to avoid accidental self-injection. Do not use in automatically powered syringes.
- Consult your veterinarian on the safe handling and use of all injectable products prior to administration.
- Micotil has a pre-slaughter withdrawal time of 42 days.

Boxed Warning

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

Human Warnings: 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 automatically 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 1-800-722-0987 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. Cardiovascular toxicity may be due to calcium channel blockade. In dogs, administration of intravenous calcium offset Micotil-induced tachycardia and negative inotropy (decreased contractility). Dobutamine partially offset the negative inotropic effects induced by Micotil in dogs. ß-adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil in dogs. Epinephrine potentiated lethality of Micotil in pigs. This antibiotic persists in tissues for several days.

AH0230 NADA 140-929, Approved by FDA

Micotil® 300 Injection*

Tilmicosin Injection, USP

Caution: 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 25% propylene glycol, phosphoric acid as needed to adjust pH and water for injection, Q.S. Tilmicosin, USP is produced semi-synthetically and is in the macrolide class of antibiotics.

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 ovine respiratory disease (ORD) associated with *Mannheimia haemolytica*. Micotil is indicated for the control 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 to 20 mg/kg of body weight (1 to 2 mL/30 kg or 1.5 to 3 mL per 100 lbs). **In sheep** greater than 15 kg, administer a single subcutaneous dose of 10 mg/kg of body weight (1 mL/30 kg or 1.5 mL per 100 lbs). Do not inject more than 10 mL per injection site.

If no improvement is noted within 48-hours, the diagnosis should be reevaluated.

For cattle and sheep, injection under the skin in the neck is suggested. If not accessible, inject under the skin behind the shoulders and over the ribs.

Note: Swelling at the subcutaneous site of injection may be observed.

Contraindications: Do not use in automatically powered syringes. Do not administer intravenously to cattle or sheep. Intravenous injection in cattle or sheep will be fatal. Do not use in lambs less than 15 kg body weight. Do not administer to 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.

Warnings:

Human Warnings: 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 automatically 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 1-800-722-0987 or 1-800-428-4441. Avoid contact with eyes.

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Advertencias Para El Ser Humano: Este producto no es para uso humano. La inyección de este medicamento al ser humano se ha asociado con muertes. Mantenga fuera del alcance de los niños. No use en jeringas operadas automáticamente. Proceda con extrema cautela para evitar la autoinyección accidental. En caso de inyección a un ser humano, consulte a un médico inmediatamente y aplique hielo o una bolsa de hielo sobre el sitio de la inyección, evitando el contacto directo con la piel. Los números de teléfono para emergencias médicas son 1-800-722-0987 ó 1-800-428-4441. Evite el contacto con los ojos.

Nota Para El Médico: El sistema cardiovascular es el blanco de la toxicidad y debe vigilarse estrechamente. La toxicidad cardiovascular puede deberse al bloqueo de los canales de calcio. En los perros, la administración intravenosa de calcio compensó la taquicardia y los efectos inotrópicos negativos (reducción de la contractilidad) inducidos por Micotil. La dobutamina compensó parcialmente los efectos inotrópicos negativos inducidos por Micotil en perros. Los antagonistas ß-adrenérgicos, como propranolol, exacerbaron el inotropismo negativo de Micotil en los perros. La epinefrina potenció la letalidad de Micotil en cerdos. Este antibiótico persiste en los tejidos por varios días.

Residue Warnings: Animals intended for human consumption must not be slaughtered within 42 days of the last treatment. Not for use in lactating dairy cattle 20 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.

For Subcutaneous Use in Cattle and Sheep Only. Do Not Use in Automatically Powered Syringes.
Solo Para Uso Subcutáneo en Bovinos y Ovinos. No Administrar con Jeringas Accionadas Automáticamente.

Precautions: Read accompanying literature fully before use. Intramuscular injection will cause a local reaction which may result in trim loss of edible tissue at slaughter. The effects of tilmicosin on bovine and ovine reproductive performance, pregnancy and lactation have not been determined.

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/ProductSafetyInformation/ucm055394.htm

Clinical Pharmacology: A single subcutaneous injection of Micotil at 10 mg/kg of body weight dose in cattle resulted in peak tilmicosin levels within one hour and detectable levels (0.07 µg/mL) in serum beyond 3 days. However, lung concentrations of tilmicosin remained above the tilmicosin MIC 95% of 3.12 µg/mL for *Mannheimia haemolytica* for at least 3 days following the single injection. Serum tilmicosin levels are a poor indicator of total body tilmicosin. The lung/serum tilmicosin ratio in favor of lung tissue appeared to equilibrate by 3 days post-injection at approximately 60. In a study with radioactive 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 10mg/kg of body weight, tilmicosin concentrations in excess of 4 µg/mL 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.

Microbiology: Tilmicosin has an *in vitro* antibacterial spectrum that is predominantly Gram-positive with activity against certain Gram-negative microorganisms. *In vitro* activity against several *Mycoplasma* species has also been observed.

Effectiveness: In a multi-location field study, 1508 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 attitude and activity, normal respiration, and a rectal temperature of <104°F on Day 13. The cure rate was significantly higher (P<0.004) in Micotil-treated calves (63.1%) compared to saline-treated calves (29.2%). During the treatment phase of the study, there were 10 BRD-related deaths in the Micotil-treated calves compared to 47 in the saline-treated calves.

Animal Safety: A safety study was conducted in feeder calves receiving subcutaneous doses of 20, 30, 40, or 60 mg/kg of body weight, injected 3 times at 72-hour intervals. Death was not seen in any of the treatment groups. Injection site swelling and mild hemorrhage at the injection site were seen in animals in all dosage groups. Lesions were described as being generally more severe and occurred at higher frequency rates in the animals treated with higher doses of tilmicosin. Lameness associated with the injection site was noted in two of twenty-four 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, 30, or 50 mg/kg of body weight, injected 3 times at 72-hour intervals did not cause any deaths. Edema at the site of injection was noted. The only lesion observed at necropsy was minimal myocardial necrosis in some animals dosed at 50 mg/kg.

In an additional safety study, subcutaneous doses of 150 mg/kg body weight injected at 72-hour intervals resulted in death of two of the four treated animals. Edema was marked at the site of injection. Minimal myocardial necrosis was the only lesion observed at necropsy. Deaths of cattle have been observed with a single intravenous dose of 5 mg/kg of body weight.

In sheep, single subcutaneous injections of 10 mg/kg body weight did not cause any deaths and no adverse effects of tilmicosin were observed on blood pressure, heart rate, or respiratory rate.

Toxicology: The heart is the target of toxicity in laboratory and domestic animals given Micotil by oral or parenteral routes. The primary cardiac effects are increased heart rate (tachycardia) and decreased contractility (negative inotropy). Cardiovascular toxicity may be due to calcium channel blockade.

Upon subcutaneous injection, the acute median lethal dose of tilmicosin in mice is 97 mg/kg, and in rats is 185 mg/kg of body weight. Given orally, the median lethal dose is 800 mg/kg and 2250 mg/kg body weight in fasted and nonfasted rats, respectively. No compound-related lesions were found at necropsy.

In dogs, intravenous calcium offset Micotil-induced tachycardia and negative inotropy, restoring arterial pulse pressure. Dobutamine partially offset the negative inotropic effects induced by Micotil in dogs. ß-adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil in dogs.

In monkeys, a single intramuscular dose of 10 mg/kg body weight caused no signs of toxicity. A single dose of 20 mg/kg body weight caused vomiting and 30 mg/kg body weight caused the death of the only monkey tested.

In swine, intramuscular injection of 10 mg/kg body weight caused increased respiration, emesis, and a convulsion. 20 mg/kg body weight resulted in mortality in 3 of 4 pigs, and 30 mg/kg caused the death of all 4 pigs tested. Injection of 4.5 and 5.6 mg/kg body weight intravenously followed by epinephrine, 1 mL (1:1000) intravenously 2 to 6 times, resulted in death of all pigs injected. Pigs given 4.5 mg/kg and 5.6 mg/kg body weight intravenously with no epinephrine all survived. These results suggest intravenous epinephrine may be contraindicated.

Results of genetic toxicology studies were all negative. Results of teratology and reproduction studies in rats were negative. The no effect level in dogs after daily oral doses for up to one year is 4 mg/kg of body weight.

Storage Conditions: Store at or below 86°F (30°C). Protect from direct sunlight.
Conservar a 86°F (30°C). Protejar de la luz solar directa.

How Supplied: Micotil is supplied in 100 mL and 250 mL multi-dose amber glass bottles.

Manufactured for:
Elanco Animal Health • A Division of Eli Lilly and Company • Indianapolis, IN 46285, USA

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