DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

March 06, 2014

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Deborah Chaleff, PhD
Director, Regulatory Affairs
Merck Animal Health
556 Morris Ave.
Summit, New Jersey 07901

RE: NADA 141-334, Zuprevo™ (tildipirosin) promotional labeling and advertisements

- ZUPREVO™ ANTIBIOTIC FAST FACTS (ZUPCA-04)
- The USA.Zuprevo.com website. (http://usa.zuprevo.com/cattle/)
- TECHNICAL BULLETIN-Preventive Efficacy of ZUPREVO 18% against *Mannheimia haemolytica* (ZUPCA-31)

Dear Dr. Chaleff:

The U.S. Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM), Division of Surveillance reviewed the promotional pieces (ZUPCA-04, ZUPCA-31) and the website http://usa.zuprevo.com/cattle/ for Zuprevo™ (tildipirosin) injection for cattle, NADA 141-334. We note that the promotional materials mentioned above are identical to promotional materials currently available on this website

As explained in more detail below, these materials are false or misleading because they make unsubstantiated effectiveness claims, and minimize or omit the risks associated with Zuprevo™. Therefore, these materials misbrand Zuprevo™ within the meaning of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and make its distribution violative of the FD&C Act.

Omission and Minimization of Risk Information

1. Human Safety Information

Zuprevo™ is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*, in beef and non-lactating dairy cattle and for the control of respiratory disease in beef and non-lactating dairy cattle at high risk for developing BRD-associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni*. The approved package insert for Zuprevo™ contains risk information including a Warning statement that reads exactly as follows:

"WARNINGS: FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. TO AVOID ACCIDENTAL INJECTION, DO NOT USE IN AUTOMATICALLY POWERED SYRINGES WHICH HAVE NO ADDITIONAL PROTECTION SYSTEM. IN CASE OF HUMAN INJECTION, SEEK MEDICAL ADVICE IMMEDIATELY AND SHOW THE PACKAGE INSERT OR LABEL TO THE PHYSICIAN."

However, the materials reviewed by CVM do not include the Warning statement information regarding risks to humans.

Further, on the Zuprevo™ website, the Human Safety statement (found under the section entitled "Treatment and Dosing)" is preceded by the sentence, "Just as Zuprevo is safe for animals, it is safe for humans when used as directed." This contradicts the risk information on the approved labeling which specifies important risks for humans administering the drug to animals.

2. *Animal Safety Information*

The Animal Safety section in the approved package insert for Zuprevo™ reads exactly as follows:

> **"ANIMAL SAFETY:** A target animal safety study was conducted using Zuprevo™ 18% administered in 5-month-old cattle as three subcutaneous doses of 4, 12, or 20 mg/kg BW given 7 days apart (1X, 3X, and 5X the labeled dose). Animals remained clinically healthy during the study at the labeled dose. Injection site swelling and inflammation, initially severe in some animals, was observed that persisted to the last day of observation (21 days after injection). No other drug-related lesions were observed macroscopically or microscopically at the labeled dose. A separate injection site tolerance study was conducted using Zuprevo™ 18% in 5- to 9-month-old cattle administered as a single subcutaneous injection of 10 mL. Injection site swelling and inflammation, initially severe in some animals, was observed that persisted to the last day of observation (35 days after injection). No other drug-related clinical signs were observed."

The risk of potentially severe injection site swelling and inflammation is not mentioned under the Animal Safety section of the website. Instead, this risk information is placed at the very bottom of the webpage, in smaller font.

Further, the Warnings section of the approved labeling contains the statement:

"DO NOT USE ZUPREVO 18% IN SWINE. Fatal adverse events have been reported following the use of tildipirosin in swine. NOT FOR USE IN CHICKENS OR TURKEYS."

We note that there is an "Important Safety Information" statement included in these promotional materials; however, the "Important Safety Information" statement located on all of the promotional pieces cited in this letter excludes the information regarding fatal adverse events in swine.

Thus these materials omit warning information and do not contain a true statement of information related to side effects, contraindications and effectiveness (se 21 CFR 202.1(e)(1)). By failing to include this information, they also suggest that Zuprevo™ is safer than has been demonstrated by substantial evidence or substantial clinical experiences (see 21 CFR 202.1(e)(6)(i)). Finally, the placement of risk information at the bottom of the webpage in smaller font fails to present this information with prominence and

readability comparable with the presentation of information related to the effectiveness of Zuprevo™ (202.1(e)(7)(viii)). Therefore these materials cause the product to be misbranded under sections 502(a) and 502(n) of the FD&C Act (21 U.S.C. §§ 352(a) & (n)). Under section 301(a) of the FD&C Act (21 U.S.C. § 331(a)), a misbranded animal drug may not be introduced or delivered for introduction into interstate commerce.

Unsubstantiated Effectiveness Claims

1. ***Duration- 28 days based on concentration in lung tissue for optimal efficacy.***

The website and Zuprevo™ Antibiotic Fast Facts contain suggestions that Zuprevo is effective for 21 or 28 days. For example, the http://USA.Zuprevo.com website contains the following statements:

> "Concentrates in the Lungs for 28 Days," "Lasts 28 days in lungs for optimal efficacy," and "Zuprevo (tildipirosin) antibiotic — an effective new macrolide — concentrates in the lungs for 28 days…and in bronchial fluid for 21 days…to control and treat BRD."

The claim of "28 days duration" appears to be based on pharmacokinetic data from the in vivo study cited on the U.S. website and in the Zuprevo™ Antibiotic Fast Facts. (Menge, M. et al., Pharmacokinetics of tildipirosin in bovine plasma, lung tissue, and bronchial fluid [from live, non-anesthetized cattle]. *J Vet Pharm Therap.* DOI: 10.1111/J. 1365-2885, 2011. 1349.x). However, in the Results section of this cited study, the authors do not conclude that duration of tildipirosin in lung tissues results in greater or optimal efficacy and, in fact, the authors conclude that "further research is warranted to gain deeper insight into the Pharmacokinetic (PK)/Pharmacodynamics (PD) relationship of tildipirosin."

In the Effectiveness section of the Freedom of Information (FOI) Summary for Zuprevo™, treatment success was determined based on observations up to 14 days post treatment with tildipirosin. Duration of clinical effectiveness beyond 14 days was not evaluated for this product. Although bronchial fluid concentration was demonstrated to be present for up to 21 days, this observation should not be confused with duration of clinical effectiveness.

Because the website and Zuprevo™ Antibiotic Fast Facts suggest that Zuprevo™ is more effective than has been demonstrated by substantial evidence or substantial clinical experience (21 CFR 202.1(e)(6)(i)), they cause the drug to be misbranded under sections 502(a) and 502(n) of the FD&C Act (21 U.S.C. §§ 352(a) & (n)). Under section 301(a) of the FD&C Act (21 U.S.C. § 331(a)), a misbranded drug may not be introduced or delivered for introduction into interstate commerce.

2. ***"TECHNICAL BULLETIN-Preventive Efficacy of Zuprevo™ 18% against Mannheimia haemolytica" (ZUPCA-31)***

The technical bulletin implies that Zuprevo™ 18% is effective for prevention of BRD and/or a primary *Mannheimia haemolytica* infection if used 5 days before shipment or a disease challenge. However, the study used to support this claim did not demonstrate that the drug prevented BRD related to a *Mannheimia haemolytica* infection for the following reason:

Disease prevention is inhibiting the introduction of disease into an area, herd, or individual. The drug did not prevent disease as all animals in the study demonstrated clinical signs of disease after being challenged with the bacterial isolate following administration of tildipirosin.

Further, the study was a model-challenge treatment study with only one bacterial species (*Mannheimia haemolytica)* and not a treatment or control of BRD study. BRD is a multi-pathogen and multi-factorial disease process which was not represented in this model challenge study. This study did not include shipment stress or other confounding factors that are important contributing factors to the BRD complex.

In addition, this study was conducted using a small number of animals (6 in each treatment group); concluding that a product will be effective in a clinical setting based on results from a small model-challenge treatment study such as this is misleading. Larger clinical studies are necessary to demonstrate clinical effectiveness.

The use of this non-clinical study as evidence to support additional claims of effectiveness in a clinical setting suggests clinical significance when in fact no such clinical significance has been demonstrated (see 21 CFR 202.1(e)(6)(vii)). Therefore this material causes the product to be misbranded under sections 502(a) and 502(n) of the FD&C Act (21 U.S.C. §§ 352(a) & (n)). Under section 301(a) of the FD&C Act (21 U.S.C. § 331(a)), a misbranded drug may not be introduced or delivered for introduction into interstate commerce.

Further, we note that administration of tildipirosin to cattle 5 days before shipment or 5 days before a disease challenge could increase the risks for human food safety and for the treated animals for the following reasons:

1. Zuprevo™ is a macrolide and has an overall risk assessment of high for antimicrobial resistance (see FOI summary, Human Food Safety [Microbial Food Safety] section). The specific approved conditions of use for this product were important factors considered when assessing the human food safety risk associated with use of this product.

   The use of alternative treatment regimens such as that suggested in these promotional materials was not considered during this assessment. The risk of development of antimicrobial resistance to this important antibiotic may increase due to increased use of Zuprevo for prevention of disease in addition to the approved uses. This could result in an increased risk to consumers of food derived from treated animals.

2. The sponsor provides no evidence to support the claim that administering tildipirosin to cattle 5 days before shipment or disease challenge will prevent BRD. Therefore, there is a significant risk that this treatment regimen will not protect cattle against BRD. This may have a serious impact on target animal health and safety because producers may not utilize other proven management or treatment measures to protect cattle from respiratory disease associated with shipment.

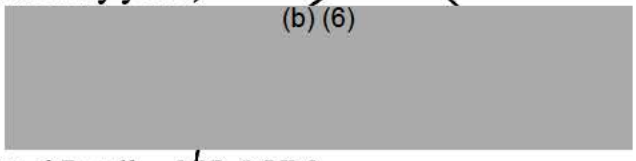
Conclusion and Requested Action

Merck Animal Health, Inc. should immediately cease misbranding Zuprevo™ promotional items described above.

The violations cited in this letter do not necessarily constitute an exhaustive list. It is your responsibility to assure that your promotional materials for Zuprevo™ comply with all the requirements of the FD&C Act and its implementing regulations. You should take prompt action to correct the violations cited in this letter. Failure to correct the violations discussed above may result in enforcement action by FDA without further notice, including seizure and injunction.

Please submit a written response within thirty (30) calendar days of receipt of this letter describing how you intend to comply with this request, listing any promotional materials for Zuprevo™ that contain statements such as those described above, and explaining your plan for discontinuing use of such materials or, in the alternative, your plan to cease distribution of Zuprevo™. If you cannot complete corrective action within 30 calendar days, state the reason for the delay and the time within which you will complete the correction. Please direct your response to Dr. Dorothy McAdams at the Food and Drug Administration, Center for Veterinary Medicine, Division of Surveillance, HFV-216, 7519 Standish Place, Rockville, Maryland 20855.

Sincerely yours,



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