Finding of No Significant Impact (FONSI)
for
PULMOTIL AC
(Tilmicosin)
in
Swine
for
the Control of Swine Respiratory Disease

Elanco Animal Health
Greenfield, IN

The Center for Veterinary Medicine (CVM) has considered the potential environmental impact of this action and has concluded that this action will not have a significant impact on the quality of the human environment and, therefore, an environmental impact statement will not be prepared.

Elanco Animal Health is requesting the approval of a supplemental new animal drug application (NADA) for the use of PULMOTIL AC in swine. This supplemental NADA will add an indication for the control of swine respiratory disease (SRD) associated with *Mycoplasma hyopneumoniae* in the presence of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) in groups of swine in buildings where a respiratory disease outbreak is diagnosed. The proposed dose is 200 mg/L in drinking water for 5 days to reach a targeted daily dose of 10 to 20 mg/kg bodyweight. The drug will be dispensed by prescription (Rx). The active ingredient in PULMOTIL AC is tilmicosin.

In support of the application, Elanco Animal Health has provided an Environmental Assessment (EA) dated January 25, 2013. A copy of the EA is attached. We have reviewed the EA and find that it supports a FONSI.

It should be noted that the final approved drug indication described above differs slightly in wording form that presented in the EA; however, this minor change in wording does not change how the end-user would interpret the indication or use the product. The minor change in wording does not impact the predicted environmental concentrations (PEC) because they were calculated based on the assumption that 100% of swine on a farm would be treated. Therefore, the slight difference in the way the indication is worded has no effect on the results or conclusions of the EA. Thus, the EA adequately evaluates the environmental risk from use of PULMOTIL AC for the currently proposed indications as described above.

The submitted EA consists of an exposure assessment that follows the recommendations presented in CVM's Environmental Impact Assessments for Veterinary Medicinal Products – Phase I (GL6) Guidance for Industry (GFI 89) and Environmental Impact Assessments for Veterinary Medicinal Products - Phase II (GL38) (GFI 166). These guidance documents were developed by the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH). The EA describes the proposed use of the product, the chemical characteristics of tilmicosin, its fate in the environment, its toxicity to and

effects on terrestrial and aquatic organisms, and a risk characterization for the use of PULMOTIL AC.

Tilmicosin is partially metabolized within swine. Elanco conducted a study on metabolism and excretion of tilmicosin in swine. After dosing swine with ^{14}C-tilmicosin, the parent compound and the T-4 metabolite were identified in the excreta. However, only the radioactivity extracted with chloroform was characterized. The radioactivity in several other solvent fractions (e.g., carbon tetrachloride, methanol/water, non-extractable fractions) was measured, but not characterized. Therefore, it is assumed in the EA that 81.8% of the administered dose is active tilmicosin after excretion. This estimate is conservative because it assumes that all non-characterized radioactivity is tilmicosin.

Degradation of tilmicosin has been studied in both manure and soil. Tilmicosin did not degrade substantially in swine manure when subjected to anaerobic conditions over 73 days. However, it has been shown to degrade very slowly in soil with an estimated half-life of approximately 2 years. Because of the uncertainty in the estimated half-life of 2 years, a more conservative half-life of 4 years was also considered in the EA and used for exposure estimates.

The predicted environmental concentrations of tilmicosin in soil (PEC_{soil}) and water (PEC_{water}) were calculated based on the expected use of the product using traditional approaches for veterinary products. These PECs were subsequently refined based on swine metabolism data (81.8% of the applied dose is considered active tilmicosin) and soil half-life data. Accumulation in soil was estimated assuming both a 2-year and a 4-year degradation half-life. The 10-year cumulative PEC_{soil} values based on a 2-year and 4-year tilmicosin half-life in soil were 916 µg/kg and 1434 µg/kg, respectively. The 10-year cumulative PEC_{water} values were 2.3 µg/L and 3.6 µg/L, respectively.

The environmental effects and toxicity of tilmicosin have been well studied in a variety of organisms. Terrestrial toxicity studies with tilmicosin have been conducted on soil microorganisms, earthworms (*Lumbricus terrestris* and *Eisenia fetida*), and plants (perennial ryegrass [*Lolium perenne*], soybeans [*Glycine max*], tomato [*Lycopersicon esculentum*], cucumber [*Cucumis sativus*], wheat [*Triticum aestivum*], and corn [*Zea mays*]). Aquatic toxicity studies have been conducted on three species of algae (*Nostoc sp.*, *Anabaena flos-aquae*, and *Pseudokirchneriella subcapitata*), the water flea (*Daphnia magna)*, and fish (bluegill [*Lepomis macrochirus*] and rainbow trout [*Oncorhynchus mykiss*]). Based on the results of these toxicity tests, the most sensitive terrestrial and aquatic species are the cucumber and a green algae, respectively. The predicted no effects concentrations (PNEC) calculated for these two species are 908 µg/kg and 0.84 µg/L, respectively.

The risk quotients for cucumber, defined as the 10-year PEC/PNEC ratio, are determined to be 0.3 (assuming a 2-year degradation half-life in soil) and 0.5 (assuming a 4-year degradation half-life in soil). The corresponding risk quotients for algae are 0.6 and 0.9, respectively. These risk quotients are less than one, even when making highly conservative exposure assumptions, indicating little or no potential for effects on terrestrial and aquatic organisms.

Based on the information in the EA, no significant environmental impacts are expected from the proposed use of PULMOTIL AC in swine for the control of SRD associated with *Mycoplasma hyopneumoniae* in the presence of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) in groups of swine in buildings where a respiratory disease outbreak is diagnosed.

{see appended electronic signature page}

_____

Steven D. Vaughn, DVM
Director, Office of New Animal Drug Evaluation, HFV- 100
Center for Veterinary Medicine
U.S. Food and Drug Administration

Electronic Signature
Addendum for Submission ID

Signing Authority (Role)	Letter Date
Steven Vaughn (Office Director)	7/13/2015

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.