Finding of No Significant Impact (FONSI)

for

Inteprity™
(avilamycin Type A medicated article)

For the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler chickens

Elanco US Inc.
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. Therefore, an environmental impact statement will not be prepared.

Elanco US Inc. is requesting the approval of a supplemental new animal drug application (NADA) to update the caution statement on the label of Inteprity™ (avilamycin Type A medicated article) to allow treatment administration to begin on or before 18 days of age rather than beginning treatment on or before 10 days of age. There are no proposed changes to the approved species, indication, dose, or duration. Inteprity™ is currently approved under NADA 141-439 for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler chickens. Avilamycin is to be fed at a concentration of 13.6 to 40.9 grams per ton in final feed (15 to 45 ppm) as the sole ration for 21 consecutive days. Inteprity™ is prescribed under a veterinary feed directive (VFD).

In support of the application, Elanco US Inc. has provided an Environmental Assessment (EA) dated January 2018. We have reviewed the EA and found that it supports a FONSI. The EA evaluates the potential environmental impacts from the proposed use of avilamycin (an orthosomycin antibiotic) in broiler chickens. The EA includes a description of the proposed use of the product, the chemical characteristics of avilamycin, fate and effects assessments, and a risk characterization.

Risk Assessment for Terrestrial and Aquatic Species

The EA generally follows recommendations in the CVM guidance documents: Environmental Impact Assessments for Veterinary Medicinal Products – Phase I (Guidance for Industry [GFI] 89) and Phase II (GFI 166). These guidance documents were developed by the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH). Briefly, Elanco estimated the predicted environmental concentrations (PEC) in litter, soil (PEC_{soil}), and water (PEC_{water}), and the predicted no effects concentrations (PNEC) for a variety of terrestrial and aquatic organisms using proprietary study data. To characterize the risk, the risk quotient (RQ) method was used in which PEC values are divided by the PNEC values (RQ = PEC/PNEC). If the RQs are below one, no additional analysis is needed.

In the exposure assessment, the initial PEC_{soil} from application of chicken litter to soil and initial PEC_{water} from soil runoff were estimated based on the expected use of avilamycin in broiler chickens. The initial PEC_{soil} and PEC_{water} were calculated to be 197 µg/kg soil and 2.2 µg/L, respectively. Although avilamycin is expected to be metabolized and degraded rapidly in the environment (see paragraph below), a total residue approach was used in the risk assessment whereby no refinements were used to reduce the PEC_{soil} or PEC_{water}. In this highly conservative approach, the underlying assumption is that the metabolites have the same toxicity as the parent compound.

Avilamycin was found to be rapidly metabolized in chickens with 78-96% of the administered dose being excreted within 4 days. However, the metabolites of avilamycin excreted from chickens have not been characterized or identified. Avilamycin also undergoes rapid dissipation in water and soil. The hydrolysis half-life of avilamycin incubated in water in the dark ranged from 0.5 to 9.6 days. The aerobic dissipation half-life (DT_{50}) measured in four different soil types (loam, loamy sand, and two sandy clay loams with varying pH and organic matter content) ranged from 0.2 to 1.5 days, while the time for 90% of avilamycin to dissipate (DT_{90}) in soil ranged from 0.6 to 28.6 days. If these data had been used to refine the PEC values for avilamycin, the values would have been lower.

In the effects assessment, acute effects data are summarized for terrestrial plants (corn, oat, radish, soybean, sugar beet, and tomato), earthworms, sewage microorganisms, blue-green algae (*Synechococcus leopolinesis*), aquatic invertebrates (*Daphnia magna*), and fish (bluegill and rainbow trout) exposed to avilamycin. From these data, Tier A (acute) PNEC values were derived using an effects endpoint (e.g., LC_{50}, the concentration producing 50% lethality in the test population) divided by an assessment factor. The most sensitive terrestrial and aquatic species were plants and blue-green algae, which had PNEC values of >5000 µg/kg and 22.8 µg/L, respectively.

In the risk characterization, the highest RQs for terrestrial (plants) and aquatic (algae) species were 0.04 and 0.10, respectively. Based on these data, Tier A RQs were less than one for all species and exposure scenarios tested. RQs less than one indicate that no significant impacts are expected from avilamycin in the terrestrial or aquatic environments.

Cumulative Impacts Assessment

The EA did not include an evaluation for potential cumulative impacts to occur from the use of avilamycin (1) for multiple indications in the same animals on the same farm, (2) in different species on the same farm, or (3) in the same or different species on different farms in the same watershed. Therefore, CVM considered the potential for the environmental introduction of avilamycin from multiple approved animal drugs containing avilamycin and the possibility for cumulative impacts.

The first scenario, which considered the potential use of avilamycin for multiple indications in the same animal on the same farm, is not expected to occur from this supplemental approval of Inteprity™ in broiler chickens because there is only one indication approved for use in chickens and the effect of the supplement is only to revise the caution statement advising when treatment administration must begin. The dose, duration, and indication for the supplemental approval is the same as the original approval of Inteprity™ for use in broiler chickens and no new classes of animals were added.

For the second and third scenarios, the use of multiple avilamycin drug products in different species on the same farm and on different farms in the same watershed was considered. Avilamycin is currently approved for use in swine (Kavalut™) and chickens (Inteprity™). EAs and FONSIs were prepared for both approvals using the assumption that 100% of the flock

or herd are treated. The PEC_{soil} and PEC_{water} values from use in swine were 1670 µg/kg and 18.8 µg/L, respectively, based on a total residue approach (i.e., no refinements for metabolism, soil adsorption or degradation). The highest RQ values from the use in swine were 0.33 and 0.82, for terrestrial (plants) and aquatic (algae) species, respectively, which are greater than RQ values from use in chickens (see above). This use in swine represents the scenario that poses the greatest risk for environmental impacts and it was concluded that this use will not pose a substantial risk to non-target organisms at the farm or watershed scale. Additionally, concentrations of avilamycin from the approved uses in chickens and swine will not be additive in soil or water. In soil, manure from swine and chickens would not be applied to the same plot of land at the same time. In water, the total mass of the drug may increase going downstream in the watershed from additional farm inputs, but the concentration will never exceed that of the maximum PEC from the farm posing the greatest environmental risk (i.e., swine scenario). Further, there would typically be additional dilution in the watershed due to runoff from sources that do not contain avilamycin (e.g., non-farm water sources) that would reduce the PEC values. Therefore, based on CVM's evaluation, there would be no potential for cumulative impacts to occur on a single farm or within a watershed from the supplemental approval of Inteprity™ in broiler chickens.

Regulatory Conclusion

Based on the information and analysis in the Inteprity™ EA, no significant environmental impacts are expected from the proposed use of avilamycin in broiler chickens.

{see appended electronic signature page}

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U.S. Food and Drug Administration

Electronic Signature
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Signing Authority (Role)	Letter Date
Matthew Lucia (Office Director)	6/25/2018

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