Finding of No Significant Impact (FONSI)
for
Maxiban™ 72™
(narasin and nicarbazin Type A medicated article)
in
Broiler Chickens

for
the prevention of coccidiosis in broiler chickens caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*

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 and, therefore, an environmental impact statement will not be prepared.

Elanco US Inc. is requesting the approval of a supplemental new animal drug application (NADA) for Maxiban™ 72™ (narasin and nicarbazin Type A medicated article) to revise the tissue residue tolerance for nicarbazin and to reduce the withdrawal period from five to zero days; there are no proposed changes to the approved species, indication, or dosage. Maxiban™ 72™ is currently approved under NADA 138-952 for the prevention of coccidiosis in broiler chickens caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*. Maxiban™ 72™ contains a 1:1 ratio of narasin and nicarbazin in the Type A medicated article is administered to broiler chickens continuously in complete feed as the sole ration to provide 27 to 45 grams each of narasin and nicarbazin.

In support of the application, Elanco US Inc. has provided an Environmental Assessment (EA) dated September 2017. A copy of the EA is attached. We have reviewed the EA and find that it supports a FONSI.

The EA evaluates the potential environmental impacts from the proposed use of narasin and nicarbazin in broiler chickens. Nicarbazin is a complex of 4,4-diniotrocarbanilide (DNC) and 2-hydroxy-4,6-dimethylpyrimidine (HDP) when administered as a drug. DNC is the active component and HDP is used to increase bioavailability (i.e., absorption) of DNC from the gut. In the target animal, the nicarbazin complex dissociates and DNC and HDP are excreted separately. The complex will not reform in the environment. Therefore, the EA contains separate risk assessments for narasin, DNC, and HDP.

The EA includes a description of the product and its proposed uses, fate and effects assessments, and a risk characterization. The EA also evaluates the potential effects of nicarbazin (specifically DNC) in non-target avian species, and the potential for cumulative impacts from multiple approvals of animal drug products containing narasin and nicarbazin.

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 organisms using proprietary study data. The PEC was compared to the PNEC to determine the risk quotient (RQ = PEC/PNEC). If the RQ is below one, no additional analysis is needed. Conversely, if the RQ is above one, additional analysis may be needed.

In the exposure assessment, the initial PEC_{soil} from application of chicken litter to soil and PEC_{water} from soil runoff were estimated for each of the three compounds (narasin, DNC, and HDP), and then, refined with available fate data, such as metabolism in the target animal, and degradation, adsorption, and accumulation in soil.

Narasin is extensively metabolized in chickens, with approximately 5% of the parent compound excreted. Narasin also degrades in chicken litter (mean degradation half-life [DT_{50}] of 7 days) and soil (mean DT_{50} of 66 days). Initial PEC_{soil} and PEC_{water} were refined for narasin using chicken metabolism data and degradation in litter data; however, the soil degradation data was not used. The refined PEC_{soil} and PEC_{water} for narasin are 27 µg/kg soil and 0.1 µg/L, respectively.

The initial PEC_{soil} and PEC_{water} for HDP are 194 µg/kg soil and 0.7 µg/L, respectively. The PEC values were not refined in the EA to account for potential metabolism, degradation or adsorption. HDP was found to degrade rapidly in soil with a mean DT_{50} of 5.3 days, but this data was not used in the EA to refine the PEC values. If these data had been used, the PEC values for HDP would have been lower.

The initial PEC_{soil} and PEC_{water} for DNC after a single application are 454 µg/kg soil and 1.7 µg/L, respectively. However, DNC was found to be persistent and immobile in soil with a mean soil DT_{50} of 230 days. Due to the potential for DNC to accumulate in soil over time after multiple annual applications of chicken litter, a plateau PEC_{soil} (after 10 years of annual applications) was calculated to be 725 µg/kg soil. Thus, the refined PEC_{water} for DNC, which accounted for accumulation and adsorption in soil, was estimated to be 0.7 µg/L.

In the effects assessment, acute effects data are summarized for terrestrial organisms (soil microflora, plants, and earthworms) and aquatic organisms (algae, *Daphnia magna*, and fish) for each compound. 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. To characterize the risk, the risk quotient (RQ) method was used in which PEC values (initial or refined) are divided by the PNEC values. Based on these data, Tier A RQs are less than one for all exposure scenarios for narasin, HDP, and DNC, except for plants exposed to HDP and DNC, and for *Daphnia magna* and fish exposed to DNC. Scenarios resulting in RQ values greater than one were further evaluated in a Tier B (chronic) risk assessment using the same RQ method. The Tier B assessment utilized data generated in studies on additional plant species exposed to HDP or DNC and reproductive data from *D. magna* and fish (*Pimephales promelas*) exposed to DNC. All Tier B RQs are less than one. An RQ less than one indicates that no significant impacts in the terrestrial or aquatic environments are expected from narasin, HDP, or DNC.

Exposure Assessment for Non-Target Avian Species

In addition to the Tier A and B risk assessments, the EA includes a quantitative evaluation of the potential risk of nicarbazin exposure to non-target avian species that could ingest soil and/or food sources (e.g., earthworms) in fields where chicken litter containing nicarbazin could be applied. This route of exposure was evaluated because nicarbazin, a pesticide registered with the United States Environmental Protection Agency[1], is known to interfere with the formation of the vitelline membrane (which separates the egg yolk and egg white), and ultimately results in reduced hatchability of avian eggs. Additionally, although nicarbazin is in the complexed form (DNC-HDP complex) when used as a pesticide, it is expected that the dissociated mixture of DNC and HDP will be present in chicken litter following excretion and will not reform the DNC-HDP complex in the environment. Studies summarized in the EA demonstrate that DNC, alone or in a mixture with HDP, is less bioavailable, and therefore, less toxic, than the DNC-HDP complex that forms nicarbazin. Therefore, exposure to a mixture of DNC and HDP in chicken litter on agricultural fields will pose a lower risk than exposure to the DNC-HDP complex. Based on the quantitative evaluation and bioavailability data provided in the EA, significant environmental impacts to non-target avian species are not anticipated from this route of exposure.

Cumulative Impacts Assessment

Finally, the EA included a cumulative impacts assessment that evaluated the environmental introduction of narasin or nicarbazin from the use of multiple approved animal drug products. It was concluded that there would be no potential for cumulative impacts from (1) use of narasin or nicarbazin for multiple indications in the same animals on the same farm, (2) use of the drugs in different species on the same farm, or (3) use of the drugs in the same or different species on different farms in the same watershed. Because the concentration of narasin and nicarbazin in Maxiban™ 72™ is the same as or lower than the concentration of narasin and nicarbazin approved for use in other animal drug products, PEC values within the watershed would not increase from those estimated in this EA. The PEC values calculated in this EA account for the worst-case farm in the watershed and concentrations in water will not be additive[2]. In addition, there would typically be additional dilution in the watershed due to runoff from sources that do not contain narasin or nicarbazin (e.g., non-farm water sources) that would reduce the PEC value. Therefore, there would be no potential for cumulative impacts to occur from the use of Maxiban™ 72™ on a single farm or within a watershed.

Regulatory Conclusion

Based on the information and analysis in the Maxiban™ 72™ EA, no significant environmental impacts are expected from the proposed use of Maxiban™ 72™ for the prevention of coccidiosis in broiler chickens.

{see appended electronic signature page}

Kevin J. Greenlees, PhD, DABT
Acting Director, Office of New Animal Drug Evaluation
Center for Veterinary Medicine
U.S. Food and Drug Administration

[1] Nicarbazin is a registered pesticide for egg hatch reduction in resident Canada geese (*Branta canadensis*). United States Environmental Protection Agency. November 2005. Nicarbazin Pesticide Fact Sheet.
[2] 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 worst-case farm input.

Electronic Signature
Addendum for Submission ID

Signing Authority (Role)	Letter Date
Kevin Greenlees (Office Director) - Acting	5/14/2018

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