Finding of No Significant Impact (FONSI)
for
Experior™
(lubabegron Type A medicated article)
for
reduction of ammonia gas emissions per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed

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 adverse 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 new animal drug application (NADA) for the use of Experior™ (lubabegron Type A medicated article), containing the active ingredient lubabegron fumarate, for reduction of ammonia gas emissions per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed. Experior™ will be used in complete Type C medicated feed at 1.25 to 4.54 g/ton (90% dry matter basis) for a minimum of the last 14 days up to a maximum of the last 91 days prior to slaughter.[1] It will be dispensed over the counter (OTC).

In support of the application, Elanco US Inc. has provided an environmental assessment (EA) for Experior™ dated June 2018. A copy of the EA is attached. We have reviewed the EA and find that it supports a Food and Drug Administration FONSI.

Experior™ is thought to act by increasing nitrogen (amino acid) uptake in beef cattle and increasing the amount of nitrogen retained in the animal as protein, thereby reducing the amount of urea excreted and contained in manure (urine and feces combined). The urea in manure is rapidly converted by an enzyme, urease, to ammonia and ammonium.[2] Subsequently, this ammonia is volatilized (i.e., released as a gas) to the atmosphere. Thus, the reduction in excreted urea from the animal results in a reduction in ammonia gas emissions to the environment.

The EA includes two environmental impact analyses for the use of lubabegron in beef steers and heifers fed in confinement for slaughter. The first analysis addresses the introduction and effects of residues of lubabegron in terrestrial and aquatic systems through its excretion in manure. The second analysis addresses the potential environmental effects, both adverse and beneficial, from the intended use of lubabegron to reduce ammonia gas emissions.

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[1] The maximum dose per head of beef cattle (hd) used in the EA (90 mg/hd/d) is based on the assumption that daily intake would consist of 90% dry matter.

[2] Ammonia (NH_3) and ammonium (NH_4^+) can interconvert and exist in equilibrium in manure. The distribution of NH_3:NH_4^+ in that equilibrium is dependent on the pH of the manure.

Effects of Lubabegron Residues in the Environment

For this evaluation, the EA described the use of Experior™ and lubabegron's chemical characteristics, fate in the environment, effects on non-target terrestrial and aquatic organisms, and the potential risks for impacts to these organisms. Where applicable, this evaluation generally followed recommendations in CVM's Guidance for Industry (GFI) 166 (Environmental Impact Assessments for Veterinary Medicinal Products – Phase II). Elanco estimated the predicted environmental concentrations (PEC) of lubabegron in manure, soil, and surface water and the predicted no effects concentrations (PNEC) for a variety of organisms using Elanco-owned study data. The PEC values were then compared to an appropriate PNEC to determine a risk quotient (RQ = PEC/PNEC). If the RQ is below one, no additional analysis is needed.

The primary route of environmental exposure to lubabegron is from excretion of lubabegron in beef cattle manure (urine and feces combined). Manure is typically removed from animal pens and applied to fields as fertilizer. Some residues of lubabegron in manure and soil may subsequently run off to surface waters during rain events. Thus, both the terrestrial and aquatic environments may ultimately be affected by lubabegron.

In the exposure assessment, Elanco used traditionally accepted methods to calculate the PEC of lubabegron in manure (PEC_{manure}), soil (PEC_{soil}), and surface waters ($PEC_{surface\ water}$) based on the proposed use pattern, and refined them using environmental fate data. Elanco provided data to demonstrate that lubabegron adsorbs strongly to soils and sediments and degrades slowly in soils. Elanco reported a soil adsorption coefficient (K_{oc}) of 47,347 to 370,420 mL/g and demonstrated that 93.1 to 93.7% of lubabegron adsorbed to soil. These data indicate limited mobility and bioavailability of lubabegron in terrestrial and aquatic environments. These data were used in the EA only to refine the $PEC_{surface\ water}$ by accounting for adsorption to sediment in water bodies.

Based on a degradation study in four soil types, Elanco derived a soil degradation half-life (DT_{50}) of 723 days for lubabegron. This value represents the upper 90th percentile confidence bound on the mean DT_{50}. Due to the long DT_{50} in soil, the cumulative effect of repeated application of contaminated manure to soils was considered when calculating refined PEC values. The adsorption data indicate that lubabegron has a low mobility, and will be retained in soils, and is expected to be found at low concentrations in groundwater or surface waters. The refined PEC_{soil} and $PEC_{surface\ water}$ were estimated to be 234 µg lubabegron/kg and 0.024 µg lubabegron/L, respectively.

These PEC values are considered to be conservative because they could have been further reduced using data generated by Elanco. For example, the K_{oc} data was only used to refine the $PEC_{surface\ water}$, but could have been used to further refine and reduce the PEC_{soil}. In addition, Elanco conducted a metabolism study demonstrating that lubabegron is extensively metabolized in the target animal prior to excretion. If these data had been used as refinements in the EA, they would have further reduced the PEC_{soil} and $PEC_{surface\ water}$ values.

For the effects assessment, Elanco provided acute ecotoxicity studies on a variety of terrestrial and aquatic species, including soil microorganisms, plants (corn, radish, perennial ryegrass, soybean, tomato, and wheat), earthworms (*Eisenia fetida*), algae (*Pseudokirchneriella subcapitata*), water flea (*Daphnia magna*), and rainbow trout (*Oncorhynchus mykiss*). PNEC values were calculated for each organism tested by dividing the effect concentration (e.g., a median lethal concentration) by the assessment factor as recommended in GFI 166.[3] The most sensitive species in the terrestrial and aquatic compartments were soil microorganisms (PNEC = 2,500 µg lubabegron/kg soil) and algae (PNEC = 0.25 µg lubabegron/L), respectively. In addition, the chronic effects of lubabegron on *D. magna* reproduction were also evaluated (PNEC = 1.2 µg lubabegron/L).

The RQ values, defined as the PEC:PNEC ratio, for the most sensitive species in the terrestrial and aquatic ecosystems were 0.09 (soil microorganisms) and 0.10 (algae).[4] These RQ values are well below the value of one, indicating little or no potential for significant adverse effects on terrestrial and aquatic organisms.

Additionally, a bioaccumulation assessment was performed for lubabegron because the octanol-water partition coefficient (K_{ow}) exceeded the GFI 166 threshold of 10,000 L/kg. The Veith-Kosian linear regression model was used to predict the bioconcentration factor (BCF) based on the K_{ow}. Using uptake factors, a biomagnification factor of 2, and an assessment factor of 30, a maximum dose was estimated for three surrogate predators (river otter, kingfisher, and osprey). Safety margins [i.e., the ratio of the no observed effects level (NOEL) to the maximum dose] were calculated for each predator and all values were greater than one (6.4 for river otters, 1.3 for kingfishers, 8.8 for osprey), indicating that there is no expectation of adverse effects due to bioaccumulation.

Effects of the Reduction of Ammonia Gas Emissions on the Environment

Agricultural sources (which include livestock) are the largest known source of ammonia gas emissions in the United States (U.S.) due to human activity.[5] Ammonia gas is thought to be a significant contributor to the eutrophication of waterways and the formation of atmospheric haze and noxious odors. The use of lubabegron is intended to reduce these emissions from beef steers and heifers fed in confinement for slaughter (i.e., in feedlots). Although the goal of using Experior™ to reduce ammonia gas emissions from the animal may be to provide some environmental benefit (e.g., reduced ammonia gas emissions may reduce eutrophication of water bodies, atmospheric haze, and noxious odors), it is still possible that use of the drug may have unintended adverse effects on the environment. Therefore, both the adverse and beneficial effects of the reduction of ammonia gas emissions were evaluated in the EA. These evaluations are described in the following paragraphs.

Evaluation of Adverse Effects of Reductions in Ammonia Emissions

Generally, it is expected that a reduction of ammonia gas emissions would only result in beneficial effects on the environment. However, because ammonia can easily transform or convert to other nitrogen compounds, there were concerns that the reduction in ammonia gas emissions may be due to a change in the distribution of nitrogen compounds (i.e., concentrations and/or chemical forms) in manure that could unintentionally result in adverse impacts to land, air, and/or water. For example, the reduction in ammonia gas emissions may indirectly result in an increase in the concentration of another nitrogen compound in manure, which could in turn run off and adversely affect waterways (e.g.,

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[3] GFI 166 recommends that assessment factors be used to account for uncertainties, such as intra- and inter-laboratory and species variation, the need to extrapolate from laboratory study results to the field, and from short term to long term toxicity (acute:chronic ratios).
[4] The sponsor incorrectly states in section 8.0 of the EA that the RQ for algae is 0.09. However, in Table 5-10 on page 29, they correctly state that the RQ for algae using the PEC refined for accumulation and adsorption is 0.10.
[5] USEPA. 2014. 2014 National Emissions Inventory (NEI) Data.

nitrate or nitrite) or volatilize and adversely affect the atmosphere (e.g., nitrous oxide). The relevant forms of nitrogen (i.e., ammonia and its transformation products), their relationships, and the compartments in the environment that potentially may be affected by them are shown in Figure 2 (page 33) in the EA.

To determine whether the concentrations or chemical forms of nitrogen compounds in manure might change through feeding of Experior™, lubabegron's mode of action in reducing ammonia gas emissions was considered. Available information on lubabegron's mode of action supports that the main effect of this drug is a reduction in excreted urea (and therefore volatilized ammonia gas) due to an increase in nitrogen (amino acid) uptake by beef cattle and an increase in the amount of nitrogen retained in the animal as protein. Further support is provided by data from a pilot effectiveness study conducted by Elanco that failed to show that lubabegron changed the total nitrogen, organic nitrogen, or ammonia nitrogen concentrations in manure from control levels at 48 hours after excretion.[6] Therefore, no changes to the concentrations or forms of nitrogen compounds in manure (other than reductions in urea and ammonia) are expected from the use of lubabegron. As a result, the forms of nitrogen compounds applied to land as fertilizer, running off to surface water, and/or volatilized to the atmosphere are not expected to change, and their concentrations are not expected to increase. Therefore, the reduction in ammonia gas emissions from use of Experior™ is not expected to have adverse impacts on land, air, or water.

Evaluation of Beneficial Effects of Reductions in Ammonia Emissions

As described above, the intended use of this drug to reduce ammonia emissions may prompt its use in order to provide a benefit to the environment. Ammonia emissions and ammonia transformation products (e.g., nitrous oxide, nitrates, particulate matter with aerodynamic diameters ≤ 2.5 μm) adversely affect the human environment through the eutrophication of water bodies, formation of atmospheric haze, and generation of noxious odors. Therefore, it is expected that any reduction in ammonia gas emissions would be beneficial. However, based on the data provided in the EA, supporting documents, and available literature, the magnitude and spatial scale of any beneficial effect of the reduction in ammonia gas emissions could not be quantified. This is due to 1) limitations in the design of Elanco's effectiveness studies, 2) issues with the extrapolation of results to a herd, farm, regional, or larger scale, and 3) data limitations and modeling uncertainties related to ammonia and its transformation products.

The effectiveness studies conducted by Elanco support a conclusion that ammonia gas emissions will be reduced per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter through feeding of Experior™. The effectiveness studies were not designed to measure or evaluate herd and farm scale emissions. The studies were conducted in semi-controlled facilities with only a single animal or a small group of animals. These semi-controlled facilities were not open to the environment and important environmental factors that could affect, and potentially reduce, the amount of ammonia gas volatilized from manure (e.g., rainfall, wind speed, manure management practices) were not accounted for. As a result, the accuracy and reliability of extrapolating the results of the effectiveness study to an entire herd, farm, or larger scale is questionable.

[6] The lack of reduction in ammonia nitrogen, which is the sum of ammonia and ammonium, at the 48-hour timepoint can be explained by the fact that most or all volatile ammonia would have volatilized by that time leaving only the less volatile ammonium form present in manure.

There are additional reasons why estimating the magnitude of any beneficial effects on the environment is difficult. Important information and data regarding the volatilization, transformation, fate, and transport of ammonia and its transformation products in the air, soil, and water, are currently lacking or of unknown reliability. As discussed in the EA (Section 6.0), factors affecting ammonia gas emissions are temporally dependent on site-specific factors. For example, volatilization and transformation of ammonia are dependent on temperature, pH, microbial community abundance, wind, weather and climate (local, regional, and national), manure storage and handling practices, and the administration of lubabegron (e.g., number of animals, dose, duration), which can vary geographically, seasonally, and from one feedlot to another. Therefore, the data needed to estimate the size or magnitude of reductions in ammonia gas emissions to the environment under real-world conditions are substantial and not currently available.

Another complicating issue is that ammonia reductions and beneficial effects could occur at different spatial scales. Evaluating these scales generally involves use of data generated at the individual, herd, or farm scale and applied in complex atmospheric models to make estimates at a regional or national scale. The limitations of current ammonia emissions data for making predictions at the herd and farm level have already been mentioned. Extrapolations to a larger scale would be even more unreliable. Further, the use of atmospheric modeling for making predictions at the regional or national scale presents many uncertainties. This is because once volatilized, ammonia and related nitrogen compounds can be transported and deposited to land and/or water over long distances. This allows for dispersion, dilution, and transformation processes to change the magnitude of any reduction in ammonia produced at the herd or farm scale. In addition, industrial sources, other animal husbandry operations (e.g., poultry, swine, dairy cattle), and crop agriculture (e.g., other fertilizer applications) all produce emissions of ammonia and other nitrogen compounds that affect atmospheric concentrations at the regional and national scales. These sources are not uniform across the country (e.g., feedlots are concentrated in the Midwest and Great Plains states) and thus, any modeling predictions are highly dependent on the location(s) being evaluated. Therefore, even if an estimate of farm-scale emissions could be made, the uncertainty of these estimates would be greatly increased at the regional and national scale. Several groups of experts and scientists have similarly concluded that it is not currently possible to accurately perform quantitative modeling or make reliable predictions with respect to the fate and transport of ammonia and its transformation products in the environment.[7,8]

For the many reasons discussed above, it is currently not possible to assess the significance of the environmental impacts due to the reduction of ammonia gas emissions from use of Experior™. Although the magnitude and effects of ammonia gas reductions cannot be quantified, as explained above, the reduction in ammonia gas emissions from use of Experior™ is not expected to have adverse impacts on land, air, or water. If there are any environmental effects, they are expected to be beneficial.

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[7] National Research Council. 2003. Air Emissions from Animal Feeding Operations: Current Knowledge, Future Needs. Washington, DC: The National Academies Press. https://doi.org/10.17226/10586
[8] USDA. Agricultural Air Quality Task Force White Paper. Ammonia emissions: what to know before you regulate. 2014. http://www.soils.usda.gov/wps/portal/nrcs/detail/national/air/taskforce/?cid=stelprdb1268645. Accessed on March 15, 2018.

Regulatory Conclusion

Based on the information in the EA, no significant adverse environmental impacts are expected from the proposed use of Experior™ for reduction of ammonia gas emissions per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.

{see appended electronic signature page}

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