Finding of No Significant Impact (FONSI)
for
Banamine® Transdermal
(flunixin transdermal solution)
Pour-On for Beef and Dairy Cattle
for use in the control of pyrexia associated with bovine respiratory disease and acute bovine mastitis, and the control of pain associated with foot rot in beef cattle 2 months of age and older and dairy cattle

Intervet Inc.
d/b/a Merck Animal Health
Madison, NJ

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.

Banamine® Transdermal (flunixin transdermal solution) Pour-On for Beef and Dairy Cattle is currently approved for use for the control of pyrexia associated with bovine respiratory disease and the control of pain associated with foot rot in steers, beef heifers, beef cows, beef bulls intended for slaughter, and replacement dairy heifers under 20 months of age. Intervet Inc. is requesting the approval of a supplemental new animal drug application (NADA) for Banamine® Transdermal to 1) add a therapeutic indication "for the control of pyrexia associated with acute bovine mastitis,"[1] 2) add the lactating dairy cow target animal subclass for all approved indications for Banamine® Transdermal, and 3) provide for a milk discard time. The new indication will be: "*for use in the control of pyrexia associated with bovine respiratory disease and acute bovine mastitis, and the control of pain associated with foot rot in beef cattle 2 months of age and older and dairy cattle. Not for use in beef and dairy bulls intended for breeding over 1 year of age; replacement dairy heifers over 20 months of age, dry dairy cows, dairy calves, or veal calves*." Banamine® Transdermal will be administered topically along the dorsal midline of cattle in a single dose of 3.3 mg flunixin free acid (FFA)[2]/kg body weight (bw). The drug will be dispensed by prescription.

In support of the supplemental application, Intervet Inc. has provided an environmental assessment (EA) dated September 29, 2016. A copy of the EA is attached. We have reviewed the EA and find that it supports a FONSI for the indications described above.[3]

The EA evaluates the exposure and effects of flunixin transdermal solution to non-target avian and mammalian receptors (i.e., scavenging and predatory species) that have the potential to directly, or indirectly, ingest flunixin residues. The EA includes a description of the product and its proposed uses, exposure and effects assessments, and a risk

[1] The current proposed action will not be limited to lactating cattle for the control of the pyrexia associated with mastitis as is currently stated in the EA. However, the expansion of the animal class to include other cattle classes has no impact on the results or conclusions of the EA because the calculation of risk quotient (RQ) in the EA was applicable for all cattle and not just lactating dairy cattle.
[2] The active ingredient in Banamine Transdermal is flunixin meglumine. All flunixin concentrations reported in this FONSI are of flunixin free acid (the marker residue) and not of flunixin meglumine.
[3] The EA evaluated four proposed indications, but this FONSI only addresses the proposed changes that are the subject of the current supplemental approval.

characterization for evaluating the risk of potential exposure scenarios to individual receptors of concern. Predicted doses (PDs) and predicted no effects doses (PNEDs) were derived for individually exposed receptors, and a risk characterization was performed that utilized a risk quotient (RQ) method, specifically the ratio of the PD to the PNED. Population-level and cumulative impact assessments were also evaluated.

The representative receptors of concern evaluated in the EA are magpies, red-tailed hawks, bald eagles, and coyotes. Magpies were chosen as the primary representative receptor of concern because they commonly feed on insects residing on cattle and have been reported to be affected by chemicals topically applied to the backs of cattle. Red-tailed hawks, bald eagles, and coyotes were also chosen as receptors for evaluation because they could be exposed to flunixin residues through consuming a magpie and/or scavenging the carcass of a previously treated cow. Exposures of non-target receptors to flunixin are expected to occur through either ingestion of hair from treated cattle or ingestion of a food source (i.e., carcass or prey). The six exposure scenarios evaluated in the EA, as illustrated in Figure 5-1 in the EA, include: (1) a magpie that ingests hair containing flunixin residues while perched on the back of a cow, (2) a magpie that ingests carcass tissue from a treated cow that has died, (3) a red-tailed hawk that scavenges magpies that previously consumed flunixin residues, (4) a bald eagle that scavenges carcass tissue from a treated cow that has died, (5) a coyote that scavenges magpies that previously consumed flunixin residues, and (6) a coyote that scavenges carcass tissue from a treated cow that has died.

Initial PD for Magpies, Red-tailed Hawks, Bald Eagles, and Coyotes

To calculate the initial PD for a magpie that consumes cattle hair, two primary assumptions were used. First, it was assumed that the magpie would land on a cow within 3 hours of it being treated with flunixin. The 3 hour post-treatment time point was chosen because it had the highest mean flunixin concentration in cattle hair sampled between 1 and 168 hours post-treatment (Schieber et al., 2014; see Section 5.2.1.1.2 and Appendix 10 in the EA). Second, it was assumed that, while foraging for insects in the treated area on the back of a cow, the magpie would ingest enough hair containing flunixin to fill 50% of its gizzard (by volume), which was the maximum percentage of cattle hair that was observed in the gizzards of magpies by Henny et al., 1985.[4] To estimate the actual mass of cattle hair that can fill 50% of a magpie's gizzard, Intervet first estimated the volume of a magpie's gizzard using published data, and then conducted a study (Sczensy, 2015) to quantify the mass of cattle hair that could fill this volume (Section 5.2.1.1 of the EA). Using this information, the PD for a magpie consuming cattle hair was determined to be 30.5 mg FFA/kg bw. The assumptions used to calculate the initial PD are considered worst case assumptions. Because magpies are primarily insectivorous and consume hair only incidentally, it would be highly unlikely for a magpie to consume enough cattle hair to fill 50% of its gizzard volume. It is even less likely that all of this cattle hair ingested would contain flunixin residues, not to mention residues at the highest measured concentration.

To calculate the initial PD for a red-tailed hawk and coyote that consume exposed magpies, it was assumed that their diet consisted entirely of magpies that had ingested flunixin residues as described in the exposure scenario above. It was also assumed that the magpie(s) were consumed within 1 hour of ingesting the flunixin residues, thereby allowing for some metabolism of flunixin to occur within the magpie (see Section

[4] It was unclear whether the mean and maximum percentages reported by Henny et al., 1985, were based on mass or volume. Therefore, it was conservatively assumed that the reported percentages were based on the total gizzard volume, which would result in higher PD values for magpies.

5.2.2.1.2 in the EA). The initial PDs for the red-tailed hawk and coyote in these scenarios were 2.43 and 2.55 mg FFA/kg bw, respectively. As noted previously, these assumptions are considered to be highly conservative. It would also be unlikely for a red-tailed hawk or coyote to then encounter and consume the exposed magpie(s) within one hour of the magpie ingesting the flunixin. Collectively, these initial exposure scenarios are considered theoretically possible, though highly unlikely to occur.

To calculate the initial PDs for a magpie, bald eagle, and coyote that consume the carcass of a treated cow that has recently died, residue data from liver tissues sampled at 48-hours by Crouch, 2013 (see Appendix 6 in the EA), were used. The PDs for the magpie, bald eagle, and coyote were 0.0435, 0.0170, and 0.0157 mg FFA/kg bw, respectively. These data are considered to be conservative because the liver contained the highest measured flunixin concentrations in cattle treated with flunixin transdermal solution at the 48-hour time point (see Table 4-3 in the EA). It is important to note that, under typical management practices on a farm, sick cattle that are near death would likely not be treated with Banamine® Transdermal because it would be futile to treat for the proposed indication (i.e., control of pyrexia associated with BRD) in an animal that is near death. Therefore, it is unlikely that a cow would die or be scavenged less than 48 hours after being treated with flunixin.

Predicted No Effects Dose for the Avian Species and Coyotes

Toxicity tests were not conducted in the specific avian and mammalian species evaluated in the EA. However, acute toxicity studies were conducted in northern bobwhite quail (Hubbard and Beavers, 2013) and rats (Smedley, 2013) from which data could be used to calculate PNEDs for avian species (magpies, red-tailed hawks, and bald eagles) and coyotes, respectively. The dose that resulted in 5% mortality (LD_5) in bobwhite quail (66 mg FFA/kg bw) was used to calculate the avian species PNED. Although an LD_{50} is normally used for this purpose, the LD_5 was used for avian species in this EA because it was statistically determined from the study data and is considered to represent a dose that would be protective of 95% of the exposed individuals and/or population. However, an LD_5 could not be calculated from the data in the rat study, so the acute LD_{50} in rats (100 mg FFA/kg bw) was used to calculate the coyote PNED. The PNEDs for avian species and coyotes were calculated by dividing the LD_x value by an assessment factor (AF) of 10 and 100, respectively. An AF of 10 was used for the avian species because the LD_5 can more accurately predict the minimum dose of toxicant that will produce an effect than can the LD_{50}, and it takes into account the slope of the dose-response curve; therefore, less extrapolation is needed. The resulting PNEDs for avian and mammalian receptors were 6.6 and 1.0 mg FFA/kg bw, respectively.

Risk Quotients for Initial Scenarios

When a RQ (PD/PNED) is less than one, it can be concluded that the drug does not pose a risk to non-target organisms in the environment. If the RQ is greater than or equal to one, risk cannot be excluded and further evaluation is normally recommended. Under the initial exposure scenarios, RQs were less than one for a red-tailed hawk ingesting magpies (RQ = 0.37) and for all receptors ingesting carcass tissue (RQs ≤0.016); therefore, these exposure scenarios and RQs did not need to be refined or further evaluated. RQs were greater than one under the initial scenarios for a magpie ingesting cattle hair (RQ = 4.6) and for a coyote ingesting exposed magpies (RQ = 2.55). Therefore, further evaluations were needed for these two exposure scenarios.

Further Evaluation of the Risk to Magpies and Coyotes

There is no single representative exposure scenario that can be used to capture the normal behavior of avian species or coyotes in relation to treated cattle. Therefore, Intervet further evaluated several exposure scenarios that could potentially occur with magpies and coyotes and refers to these evaluations as refined PDs and RQs (see Section 6.3 in the EA). Therefore, to be consistent, the terms refined PD and refined RQ will be used herein.

Intervet calculated eight refined PDs for magpies ingesting cattle hair by refining the two primary assumptions used to calculate the initial PD as described above. First, the amount of hair that a magpie ingests was reduced from 50 to 12% of its gizzard (by volume), although it was still conservatively assumed that all of this hair contained flunixin. The 12% value was based on the mean percentage of cattle hair in the gizzard content of magpies, as reported by Henny et al., 1985, and this is the best representation of the amount of hair a magpie could ingest based on the limited data available in the literature. Second, instead of only assuming that a magpie would ingest cattle hair 3 hours after it had been treated with Banamine® Transdermal (i.e., the time point with the highest mean flunixin concentrations in cattle hair reported by Schieber et al., 2014), a range of possible times up to 168 hours post treatment were used. Intervet relied on the flunixin residue data measured on cattle hair by Schieber et al., 2014, and assumed that a magpie could ingest hair from a treated cow at time points 1, 3, 6, 12, 14, 48, 72, or 168 hours post treatment; see Table 5-2 in the EA. This approach allowed for the evaluation of lower and more realistic exposure concentrations that a magpie could be exposed to due to the dissipation of flunixin on the cattle hair over time (i.e., the dissipation half-life (DT_{50}) on hair was 22.1 hours, see Section 5.2.1.1.2 in the EA). Based on these assumptions for calculating refined PDs, the refined RQs for magpies ingesting cattle hair ranged from 1.1 at 3 hours post treatment to 0.064 at 164 hours post treatment. Only the RQs for exposures occurring at 3 and 6 hours post treatment were at or above one (RQs equal 1.1 and 1.0, respectively).

Although two of the eight refined RQs for magpies (described above) are at or above one, the likelihood of these exposure scenarios occurring will be very low. For example, only a small fraction of a herd is expected to be treated with Banamine® Transdermal at one time so the chances of a magpie only landing, and foraging for insects, on a treated cow is low. Additionally, while it is possible for a magpie to ingest hair from a cow that has been treated with flunixin at some point in time, very sick cows that are treated with veterinary drugs are commonly housed in hospital pens or covered pens for a period of time after treatment (e.g., 24 hours) for continued observations. Therefore, it would be less likely for a magpie to interact with a cow that had been treated within the past six hours when the flunixin concentrations are high enough to pose a risk to the magpies. Therefore, we would expect that an adverse effect from a magpie ingesting cattle hair containing flunixin residues would be a rare event.

To further evaluate the potential for adverse effects on coyotes ingesting exposed magpies, Intervet evaluated thirty exposure scenarios, including the initial exposure scenario described above, using two sets of varying conditions. First, it was assumed that the percentage of cattle hair in the gizzard of the magpie(s) consumed by the coyote could range from 10 to 50% of the gizzard volume (i.e., 10, 12, 20, 30, 40, and 50%). This assumption allowed for the evaluation of a range of exposure scenarios for magpies based on the fraction of cattle hair that was assumed to be ingested by magpies under the initial and refined exposure scenarios (i.e., 50 and 12 %, respectively). Second, instead of assuming that the time interval between a magpie ingesting flunixin residues and a coyote ingesting an exposed magpie was 1 hour, it was assumed that this time interval could range from 1 to 24 hours (i.e., 1, 3, 6, 12, or 24 hours). This range of times was used because it

is not possible to predict a single time at which a magpie may experience adverse effects from flunixin (i.e., a magpie may not become morbid or die immediately after ingesting the dose of flunixin) or when a coyote might encounter this exposed magpie. The elimination half-life ($t_{1/2}$) of flunixin is quite rapid (the $t_{1/2}$ in magpies was estimated to be 2.5 hours; see Section 5.2.2.1.2 in the EA), so using a range of times between 1 and 24 hours also accounts for additional metabolism of flunixin in the magpie over time. This will result in a decrease in the exposure concentration to the coyote. Of the 30 exposure scenarios evaluated, 25 exposure scenarios, including the initial exposure scenario, resulted in RQs that were between 1.0 and <0.001, while five resulted in RQs greater than one (RQs ranged from 1.2 to 2.55; see Table 6-5 in Section 6.3.2 of the EA).

All the exposure scenarios for coyotes with RQs greater than one occurred when a magpie had ingested enough cattle hair to fill 30 to 50% of their gizzard (by volume) and when the coyote consumed the magpies within three hours of the magpie ingesting flunixin. However, a coyote would need to consume almost nine magpies in one meal (see an example calculation in Section 6.2.1 of the EA) before an RQ would be greater than one. The likelihood of these exposure scenarios occurring is considered extremely low, if not impossible. Additionally, if a coyote was exposed to a magpie that had consumed only enough cattle hair to fill 12% of its gizzard contents, as it was assumed for the refined magpie scenario previously described, the RQs would be no greater than 0.61. Therefore, we conclude that significant impacts on coyotes would be unlikely to occur.

Population Level Effects

Population level effects were also addressed in the EA (see Section 6.4 in the EA). All RQs in the EA were calculated for an individual receptor exposed to an individually treated animal. There were no RQs above one for individually exposed red-tailed hawks or bald eagles, so there would be no anticipated adverse effects at the population level for these receptors. For magpies, there were RQs above one, although it is apparent that any morbidity or mortality in these birds would be a very rare event even when using conservative assumptions in the exposure scenarios. However, it is unlikely there would be any significant negative population level effects because magpies are very common and widespread (i.e., not threatened or endangered), and their home range would extend well beyond the perimeter of any particular farm. Chronic sublethal effects, including effects on reproduction that could affect populations, are not anticipated because flunixin is rapidly metabolized. In addition, if mortality in magpies would be a rare event, then any adverse events in coyotes would also be expected to be a rare event that would not have any significant negative impacts at the population level.

Cumulative Impacts Assessment

Banamine® Transdermal is the first approval of a pour on flunixin treatment in any species. Flunixin is, however, also currently approved for use as a paste and as granules for use in horses, and as an injectable for use in horses, cattle, and sheep. Therefore, the potential for cumulative impacts to occur from the aggregate exposure of flunixin residues from multiple approved uses of Banamine® Transdermal, and from multiple approved animal drug products containing flunixin, were both considered. Based on the risk assessment in this EA for Banamine® Transdermal and the other currently approved uses of flunixin, the only potential exposure pathway that could result in cumulative exposures, and thus cumulative impacts to non-target receptors, would occur from the ingestion of carcass

tissue from treated cattle.[5] As presented in Section 6.5 in the EA, the risk to non-target receptors ingesting carcass tissue would be greatest from cattle injected with flunixin because this use pattern results in the highest concentrations of flunixin residues in the tissues (i.e., liver). However, the RQs for this use pattern are no greater than 0.048 for any non-target receptor and below a level of concern, even when assuming a worst case scenario whereby the receptor's entire diet consists of liver tissue from cattle that were treated with flunixin 48 hours prior to death. Thus, it can be concluded that there would be no cumulative exposures or impacts beyond those already evaluated in the EA.

Conclusion

Based on the data, assumptions, and calculations presented in the EA, no significant environmental impacts are expected from the proposed use of Banamine® Transdermal for use in the control of pyrexia associated with bovine respiratory disease and acute bovine mastitis, and the control of pain associated with foot rot in beef cattle 2 months of age and older and dairy cattle (not for use in beef and dairy bulls intended for breeding over 1 year of age; replacement dairy heifers over 20 months of age, dry dairy cows, dairy calves, or veal calves).

{see appended electronic signature page}

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

[5] Cumulative impacts did not need to be evaluated for the other potential exposure pathways evaluated in this EA for Banamine® Transdermal (i.e., magpies ingesting of treated cattle hair and red-tailed hawks and coyotes ingesting exposed magpies) because they could only occur from the transdermal pour on product. These exposure pathways are not possible for the paste, granules or injectable products.

Electronic Signature
Addendum for Submission ID

Signing Authority (Role)	Letter Date
Matthew Lucia (Office Director)	11/30/2022

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