Finding of No Significant Impact (FONSI)
for
Cystorelin®
(gonadorelin)

For use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows

Merial Inc.
Duluth, GA

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.

Merial Inc. is requesting the approval of a supplemental new animal drug application (NADA) for Cystorelin® (gonadorelin) for use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows. The proposed dose is 100 µg gonadorelin diacetate tetrahydrate per injection (2 ml). For the proposed indication, the first Cystorelin® injection (2 mL) is to be administered at Time 0. Cloprostenol (500 µg as cloprostenol sodium) is to be administered by intramuscular injection 6 to 8 days after the first Cystorelin® injection. The second Cystorelin® injection (2 mL) is to be administered 30 to 72 hours after the cloprostenol sodium injection. Cystorelin® will be dispensed by prescription.

In support of the application, Merial Inc. has provided an Environmental Assessment (EA) dated October 6, 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 uses of gonadorelin and cloprostenol in dairy cows and beef cows. Gonadorelin is a synthetic gonadotropin-releasing hormone (GnRH) responsible for the release of gonadotropins, luteinizing hormone, and follicle stimulating hormone from the anterior pituitary. The chemical structure of gonadorelin is identical to natural GnRH. Cloprostenol is a synthetic prostaglandin structurally related to dinoprost, a naturally occurring prostaglandin F2α (lipid compound).

The EA generally follows recommendations in the CVM guidance document: Environmental Impacts Assessment for Veterinary Medicinal Products – Phase I (Guidance for Industry [GFI] 89). This guidance document was developed by the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH). The EA includes a description of the

product and its proposed uses and the fate and behavior in the environment (primarily referencing publicly available literature). Merial estimated the predicted environmental concentrations in soil (PEC_{soil}), groundwater ($PEC_{groundwater}$), and surface water ($PEC_{surfacewater}$) based on the proposed use pattern of the animal drug.

In the exposure assessment, the initial PEC_{soil} values were calculated for gonadorelin and cloprostenol based on use in pasture and intensively reared dairy cows and beef cows. To calculate the PEC_{soil} for gonadorelin, the sponsor followed equations in the European Medicines Agency's (EMEA) guidance document (EMEA 2008[1]) and the assumption that gonadorelin is administered twice for a total of 200 µg per animal. CVM does not currently have guidance for calculating PEC values. The EMEA method was reviewed and considered appropriate for this EA. Additionally, it was assumed that the drugs have not been metabolized or degraded in the animal or environment. PEC_{soil} and $PEC_{surface\ water}$ values calculated in the EA are summarized below in Tables 1 and 2, respectively.

Table 1. Predicted environmental concentrations in soil (PEC_{soil}) for gonadorelin and cloprostenol for pasture and intensively reared cattle

	Pasture Dairy cows	Pasture Beef cows	Intensively reared Dairy cows	Intensively reared Beef cows
Gonadorelin (µg/kg)	0.00093	0.0025	0.0022	0.0038
Cloprostenol (µg/kg)	0.0023	0.0063	0.0056	0.0095

Table 2. Predicted environmental concentrations in surface water ($PEC_{surface\ water}$) for gonadorelin and cloprostenol for pasture and intensively reared cattle

	Pasture Dairy cows	Pasture Beef cows	Intensively reared Dairy cows	Intensively reared Beef cows
Gonadorelin (µg/L)	0.00057	0.0016	0.0014	0.0023
Cloprostenol (µg/L)	0.0014	0.0039	0.0034	0.0058

All PEC_{soil} and $PEC_{surface\ water}$ values are below the recommended screening exposure threshold of 100 ppb and 1 ppb, respectively, listed in CVM GFI #89, Environmental Impact Assessment for Veterinary Medicinal Products - Phase I. Therefore, we conclude that environmental impacts are unlikely to occur and no further assessment is needed.

The environmental exposure is expected to be further minimized due to extensive metabolism in the target animal and degradation in the environment. The EA summarizes publicly available literature that supports that gonadorelin and cloprostenol are rapidly absorbed in cattle (e.g., maximum plasma concentrations of gonadorelin are obtained within 15 min), undergo partial metabolism to smaller, less active peptide fragments and amino acids, and then are rapidly eliminated from the plasma, tissue, milk, and urine. Because peptides are ubiquitous and labile, even if small amounts of gonadorelin or cloprostenol are excreted unchanged, they will likely be rapidly degraded to simple peptides and amino acids by peptidases and microbes

[1] EMEA. 2008. Revised guidance on the environmental impact assessment for veterinary medicinal products in support of the VICH Guidelines GL6 and GL38. Committee for Medicinal Products for Veterinary Use (CVMP). EMEA/CVMP/ERA/418282/2005-Rev.1.

present in the soil and water environments. The ultimate rate of degradation will depend upon environmental factors, including the types and quantities of microbes, aerobic conditions, moisture content, and pH, but no persistence or accumulation of these compounds in the environment is expected.

Finally, the potential for cumulative impacts to occur from the supplemental approval of Cystorelin® was evaluated by CVM because gonadorelin and cloprostenol are approved for multiple indications in cows and heifers. Because gonadorelin and cloprostenol are only approved for use in cows and heifers for reproductive purposes, there would be no cumulative impacts from use of the drugs in different species on the same farm and it is unlikely that a single animal would be treated for multiple indications at the same time. Therefore, the only scenario further evaluated is from use of the drugs on different farms in the same watershed. Gonadorelin is approved at a dose up to 200 µg per animal and cloprostenol is approved at doses of up to 1000 µg per animal. The PEC_{soil} for gonadorelin using the maximum approved dose of 200 µg per animal (PEC_{soil} ≤0.0038 µg/kg soil), which would be the worst-case scenario, was calculated in the EA. A PEC_{soil} for cloprostenol was calculated in the EA based on a dose of 500 µg per animal, but this is not the maximum approved dose for cloprostenol. If a maximum dose of 1000 µg per animal is used in the calculation, the PEC_{soil} for cloprostenol would be no greater than 0.019 µg/kg soil. The maximum PEC_{soil} values (individually or cumulatively) are well below the threshold value of 100 µg/kg soil recommended in CVM GFI #89. Therefore, it is concluded that runoff from any combination of approved uses of gonadorelin and cloprostenol will not pose a substantial risk to non-target organisms at a farm scale or within a watershed.

Based on the information in the EA, no significant environmental impacts are expected from the use of gonadorelin with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows.

{see appended electronic signature page}

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

Electronic Signature
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