Finding of No Significant Impact (FONSI)
for
EAZI-BREED
(progesterone)
CIDR Cattle Insert
in
Dairy Cows

Zoetis
Kalamazoo, MI

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.

Zoetis (formally Pfizer Animal Health) is requesting the approval of a supplemental new animal drug application (NADA) for the use of EAZI-BREED (progesterone) CIDR Cattle Inserts. This supplement is intended to add a new indication for induction of estrous cycles in anestrous lactating dairy cows. EAZI-BREED CIDR Cattle Insert is currently approved for use under NADA 141-200 for (1) synchronization of estrus in suckled beef cows and replacement beef and dairy heifers, (2) advancement of first postpartum estrus in suckled beef cows, (3) advancement of first pubertal estrus in replacement beef heifers, and (4) concurrent use with LUTYLASE (dinoprost tromethamine) Sterile Solution for synchronization of estrus in lactating dairy cows.

In support of the supplemental application, the drug sponsor has provided an Environmental Assessment (EA) signed December 20, 2012. We have reviewed the EA and find that it supports a FONSI.

The EA describes the proposed use of the product, the chemical characteristics of progesterone, and its fate in the environment. In addition, the current EA addresses the use of the CIDR Insert to induce estrous cycles in anestrous lactating dairy cows, the impact this use may have on the on the total amount of progesterone found in the environment, and information on spatial and temporal characteristics and reproduction practices of dairy farms in the U.S. In particular, the EA addresses the potential for the active steroid ingredient, progesterone, to cause endocrine disrupting types of environmental effects in aquatic systems (i.e., reproductive effects on fish) as a result of product use.

The EA includes a detailed exposure assessment that evaluates the potential increase in environmental progesterone as a result of this new indication and use of the EAZI-BREED CIDR Insert. Previous studies indicate that only 46.3% of the 1.38 g of progesterone contained in the CIDR Insert is absorbed by the dairy cows, for a total of 91.4 mg/day, or 640 mg progesterone over the 7-day administration period. This amount (91.4 mg/day) is much less than the estimated 375 mg progesterone produced per day by dairy cows with a functional corpus luteum. Studies have also demonstrated that administration of CIDR Inserts provide approximately 1 ng/ml of additional progesterone in the plasma of lactating dairy cows, which does not exceed progesterone concentrations observed during the luteal phase of the estrous cycle (5-10 mg/ml) or during pregnancy (10-12 ng/ml). Progesterone from the CIDR Insert is indistinguishable from naturally produced progesterone, and is metabolized in the animal (*in vivo*) using the same pathways. Progesterone is extensively metabolized prior to excretion, with an estimated 1.1% of parent progesterone being excreted (i.e., 98.9% of absorbed progesterone from a CIDR Insert is metabolized). Because scientific literature has reported that progesterone could

potentially be transformed to androstenedione (AED), another possibly active hormone chemical, the EA also addresses the potential metabolism of progesterone to AED.

Available literature suggests there are multiple potential sources for progesterone in the environment; however, it does not appear that dairy cow farms are a predominant source of input. Based on a worst-case scenario in which an entire herd of dairy cows is administered EAZI-BREED CIDR Inserts at the same time, the initial predicted environmental concentrations in soil (PEC_{soil}) and water (PEC_{water}) of progesterone are estimated to be 6.69 µg/kg and 75 ng/l, respectively. However, based on the expected use for the new indication of inducing estrous cycles in anestrous lactating dairy cows, the initial PEC_{water} was refined. Refinements were based on (1) extensive metabolism of progesterone in the cow, in which only 1.1% of parent progesterone is anticipated to be excreted, (2) strong adsorption of progesterone to sediment (average K_{oc}=8248), and (3) the expectation that a maximum of 23% of the herd will be treated in a 90-day manure collection period for inducing estrous cycles. Based on these factors, the refined PEC_{water} was determined to be 0.020 ng/l progesterone. Similarly, the refined PEC_{water} for AED was determined to be 0.028 ng/l.

To date, endocrine disrupting effects of progesterone in terrestrial organisms have not been a subject of scientific or regulatory concern and are not extensively covered in this EA. Although there may be some uncertainty associated with endocrine effects on terrestrial organisms, at this time, effects are not expected.

With regard to endocrine disrupting effects in aquatic organisms, a recently published article on the potential effects of progesterone on fathead minnow reproduction was referenced in this EA. This study had several deficiencies and limitations, and therefore, is not considered adequate and reliable for use in risk assessment. However, the results of this study suggest that effects on fish fecundity may occur at concentrations as low as 10 ng/l progesterone, a level well above the refined PEC_{water} of 0.020 ng/l for progesterone.

For AED, the predicted no effects concentration (PNEC) for endocrine-related effects (masculinization in female fish) was 4 ng/l, a level much greater than the refined PEC_{water} of 0.028 ng/l.

Overall, this EA demonstrates that the use of EAZI-BREED CIDR Cattle Inserts for the induction of estrous cycles in anestrous dairy cows will contribute a very small increase in the overall environmental concentrations of progesterone. It is estimated that progesterone concentrations in surface water will increase by only 0.020 ng/l as a result of this new indication and use, and that CIDR Insert-derived progesterone represents only 0.53% of the yearly endogenous progesterone production rate in dairy cattle. This slight incremental increase is unlikely to cause reproductive effects in fish or other aquatic organisms.

Based on the information in the EA, it is concluded that no significant environmental impacts are expected from the proposed use of progesterone to induce estrous cycles in anestrous lactating dairy cows.

{see appended electronic signature page}

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Signing Authority (Role)	Letter Date
Steven Vaughn (Office Director)	3/2/2013

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