

Finding of No Significant Impact (FONSI)
for
SAFE-GUARD AQUASOL
(fenbendazole oral suspension)
in
Swine except for nursing piglets

Intervet Inc.
d/b/a Merck Animal Health
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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.

Intervet Inc. is requesting the approval of a new animal drug application (NADA) for the use of SAFE-GUARD AQUASOL (fenbendazole oral suspension)¹ in swine, except for nursing piglets, for the treatment and control of: Lungworms: Adult *Metastrongylus apri*, adult *M. pudendotectus*; Gastrointestinal worms: Adult and larvae (L3, L4 stages, liver, lung, intestinal forms) large roundworms (*Ascaris suum*); nodular worms (*Oesophagostomum dentatum*, *O. quadrispinulatum*); small stomach worms (*Hyostrongylus rubidus*); Adult and larvae (L2, L3, L4 stages - intestinal mucosal forms) whipworms (*Trichuris suis*); and Kidney worms: Adult and larvae *Stephanurus dentatus*.

SAFE-GUARD AQUASOL will be administered in drinking water at a daily dose of 2.2 mg/kg body weight (bw) for three consecutive days for a total dose of 6.6 mg/kg bw. SAFE-GUARD AQUASOL will be dispensed over the counter.

The proposed dose for SAFE-GUARD AQUASOL is lower than the approved dose of SAFE-GUARD Type A Medicated Article (3 mg/kg bw for three consecutive days) because the fenbendazole (FBZ) in SAFE-GUARD AQUASOL has been modified to reduce the particle size to ensure that the drug remains in suspension to allow administration in the drinking water. This reduced particle size resulted in an increased bioavailability within swine as compared to unmodified FBZ and, therefore, will be administered at a lower dose.

In support of the application, Intervet Inc. has provided an Environmental Assessment (EA) dated January 15, 2015. A copy of the EA is attached. We have reviewed the EA and find that it supports a FONSI.

The final wording for the established name, species, and indication in the EA are different from the label and FONSI because they were finalized after the EA was prepared and before product approval. However, these changes do not affect the outcome of the EA because there was no increase in the dose, duration, or fraction of

¹ The established name for the drug in the EA (20% fenbendazole suspension) differs from that on the product label and FONSI (fenbendazole oral suspension) because it was changed to comply with the United States Pharmacopeia (USP) nomenclature policy after the EA was prepared.

the herd treated. Therefore, the EA adequately evaluated the final indication and dosing regimen.

The EA assesses the fate and effects of FBZ and its principle primary and secondary metabolites, oxfendazole (OXF) and fenbendazole sulfone (FBZ-SO₂), respectively. The EA includes an exposure assessment from which predicted environmental concentrations (PECs) were calculated, an effects assessment from which the predicted no effects concentrations (PNECs) were derived, and a risk characterization that utilizes a risk quotient (RQ) method using the PEC/PNEC ratio.

Risk Assessment Approach

The environmental fate of the three main compounds of concern (FBZ, OXF, and FBZ-SO₂) is addressed in the EA and an initial PEC in soil (PEC_{soil}) was calculated for each compound. Although traditionally accepted methods were used to calculate the PEC_{soil} and PEC in water (PEC_{water}) for FBZ, a more complex approach was used for OXF and FBZ-SO₂. Experimental fate data suggest that, unlike FBZ, OXF and FBZ-SO₂ have the potential to persist and accumulate in the environment. Therefore, plateau PEC_{soil} values were calculated for OXF and FBZ-SO₂ to account for the possibility of accumulation in the environment following several successive years of application of manure containing these compounds to agricultural fields. While effects data were generated for FBZ and OXF, they were not generated for FBZ-SO₂ because FBZ-SO₂ is a metabolite of OXF, i.e., a secondary metabolite of FBZ. Therefore, because there were no effects data with which to calculate PNECs and RQs for FBZ-SO₂, a total residue approach was used for OXF and FBZ-SO₂ whereby individual plateau PEC_{soil} values for OXF and FBZ-SO₂ were added together (OXF/FBZ-SO₂) as a combined plateau PEC_{soil} and it was assumed that FBZ-SO₂ is as toxic as OXF. This combined plateau value was then used to calculate the PEC_{water} for OXF/FBZ-SO₂ and to calculate RQs. In the risk characterization section of the EA, separate RQs were calculated for FBZ and OXF/FBZ-SO₂. To account for the presence of all three compounds in the soil simultaneously, the two RQs were ultimately added together for a total combined RQ value for each tested organism. We based our regulatory decision on these combined RQ values.

Exposure Assessment

The exposure assessment in the EA contains the physical-chemical properties of FBZ, OXF, and FBZ-SO₂, as well as soil adsorption/desorption and soil biodegradation data. The fate data suggested that FBZ is slightly mobile to hardly mobile² while OXF and FBZ-SO₂ were considered to be moderately mobile to slightly mobile. Additionally, the dissipation half-life (DT₅₀) for FBZ ranges from 7.6 to 11.4 days (three soil types) while the DT₅₀ for OXF ranges from 123.1 to 319.4 days (three soil types) and the DT₅₀ for FBZ-SO₂ was estimated to be 186.5 and 221.3 days (two soil types).

No metabolism data were used in the EA to support the breakdown of FBZ in swine prior to excretion; it was conservatively assumed that the 100% of the administered dose was excreted as FBZ. It was assumed that, once in the soil, FBZ degrades to

² Mobility classification is based on the Food and Agriculture Organization (FAO) Mobility Classification in the EPA's Guidance for Reporting on the Environmental Fate and Transport of the Stressors of Concern in Problem Formulations (December 2009).
http://www.epa.gov/pesticides/science/efed/policy_guidance/team_authors/endangered_species_reregistration_workgroup/esa_reporting_fate.htm

OXF, which will then further degrade to FBZ-SO₂. It was also assumed that the maximum fraction of OXF and FBZ-SO₂ in the soil were the same, 64.2% of the original FBZ dose. Based on the expected use of SAFE-GUARD AQUASOL, the initial PEC_{soil} and PEC_{water} for FBZ were estimated to be 33.44 µg/kg and 0.37 µg/L, respectively. The initial PEC_{soil} for OXF and FBZ-SO₂ were each 21.4 µg/kg. These PEC_{soil} values for OXF and FBZ-SO₂ were then refined to account for accumulation in the soil over time and added together for a single plateau PEC_{soil}. The combined plateau PEC_{soil} and PEC_{water} for OXF/FBZ-SO₂ were estimated to be 105.57 µg/kg and 1.16 µg/L, respectively. No refinements were used to reduce the PEC_{soil} for FBZ or OXF/FBZ-SO₂ to account for metabolism in the animal, adsorption to soil, or degradation in the soil, water, or manure. However, the PEC_{water} was refined to account for strong adsorption to sediment. Thus, the refined PEC_{water} for FBZ and OXF/FBZ-SO₂ was estimated to be 0.039 µg/L and 0.89 µg/L, respectively.

Effects Assessment

In the effects assessment, Tier A (acute) PNEC values were derived for FBZ and OXF based on the effects in terrestrial (soil microorganisms, plants, and earthworms) and aquatic organisms (algae, *Daphnia magna*, and fish). PNEC values were derived using an effects endpoint divided by an assessment factor (AF), as recommended in CVM Guidance for Industry (GFI) 166. However, the Tier A PNEC value for fish was calculated using the results of a prolonged fish toxicity (i.e., 21-day median lethal concentration [LC₅₀] and an AF of 100) instead of the traditionally accepted endpoint for fish, a 96-h LC₅₀, and an AF of 1,000. This approach was used because the results of the prolonged toxicity test with FBZ suggested that it could take up to seven days for FBZ to come to equilibrium in the fish, resulting in a delay in toxic effects, due to its low water solubility (i.e., ~80 µg/L). A traditional 96-h acute study would not capture this observed latent toxicity and would potentially underestimate the true effects concentration. A prolonged latent toxicity test was not conducted for OXF because it does not have a low water solubility like FBZ and a 96-h LC₅₀ test was considered adequate to address the acute effects in fish. Tier B (chronic) PNEC values for *D. magna* were derived for FBZ and OXF by dividing the no observed effects concentration (NOEC) by AFs of 10 and 20, respectively. A more conservative approach was used for deriving the PNEC for *D. magna* exposed to OXF because, during the study, *D. magna* were fed three-times the amount recommended in the Organization for Economic Co-operation and Development (OECD) Guideline 211 for this test. This deviation may have increased the observed NOEC on reproduction; therefore, an AF of 20 was used instead of the standard AF of 10 to account for this uncertainty.

Risk Characterization

As described above, separate RQs were calculated for FBZ and OXF/FBZ-SO₂. The RQs were ultimately added together to generate a combined RQ value for each organism and account for the presence of all three compounds in the soil simultaneously. This is a highly conservative approach because it assumes that the mode of action of all three compounds is the same. No refinements were used to reduce the PEC_{soil}, but adsorption data were used to reduce the PEC_{water}. Tier A combined RQs were less than one for all terrestrial organisms tested (i.e., RQs for plants and earthworms were 0.621 and 0.107, respectively); therefore, Tier B studies were not needed for terrestrial organisms. Tier A combined RQs for aquatic organisms calculated with the refined PEC_{water} were less than one for algae (0.024) and fish (0.79) but greater than one for *D. magna* (19.52). Consequently, Tier B

studies were conducted exposing *D. magna* to chronic exposures of FBZ and OXF. Based on the results of the refined PEC_{water} and Tier B effects study, the combined RQ for *D. magna* was 1.12. Because RQs for *D. magna* were slightly greater than one, RQs for sediment-dwelling invertebrates was considered, as recommended in GFI 166. The RQ for sediment-dwelling invertebrates was also 1.12.

Although the RQs for aquatic invertebrates were slightly greater than one, all other RQs calculated in the EA were less than one. We consider the refined PEC_{water} values upon which these RQ values are based to be an overestimation of the potential exposure to these compounds from the use of SAFE-GUARD AQUASOL because several conservative assumptions were used, including that 1) 100% of the administered dose of FBZ was excreted by the target animal unmetabolized, 2) manure was only stored for 60 days even though more current swine manure management practices indicate a typical storage period of 90 to 180 days, and 3) 100% of the OXF will degrade to 100% FBZ-SO₂ (e.g., terminal residue) and that no other degradation or mineralization of OXF will occur. In addition, the PEC values did not take into account potential adsorption in the soil or degradation in the soil, water, and manure. Therefore, it is expected that the environmental concentrations of FBZ and its metabolites will be lower than predicted in this EA and will not present a significant risk to the environment.

Cumulative Assessment

In terms of cumulative impacts, there are several possible scenarios that could occur: (1) use of FBZ for multiple indications in the same animals on the same farm, (2) use of FBZ in different species on the same farm, and (3) use of FBZ in the same or different species on different farms in the same watershed.

To evaluate these scenarios, CVM considered the potential for the environmental introduction of FBZ from multiple approved animal drug products containing FBZ (i.e., SAFE-GUARD Type A Medicated Article, SAFE-GUARD Suspension 10%, PANACUR Suspension 10%, SAFE-GUARD 10% Paste, PANACUR 10% Paste, and SAFE-GUARD ENPROAL medicated feed block). For comparison purposes, maximum PEC_{soil} values from use of FBZ in beef cattle, dairy cattle, turkeys, and swine were calculated by CVM to be 25.3, 26.1, 31.0 and 45.6 µg/kg soil, respectively, based on the methods used in the current EA. Based on this analysis, SAFE-GUARD Type A Medicated Article for swine would result in the highest PEC_{soil} (45.6 µg/kg) and highest refined PEC_{water} (0.05 µg/L) compared to all other FBZ products, including SAFE-GUARD AQUASOL (PEC_{soil} = 33.44 µg/kg). Using the refined PEC_{water} value and the effects data for *D. magna*, the RQ for SAFE-GUARD Type A Medicated Article would be slightly higher than the RQ for SAFE-GUARD AQUASOL (i.e., the RQ would be 1.5 versus 1.12). However, like the RQ value for SAFE-GUARD AQUASOL, we think that this value is an overestimation due to the conservative assumptions used to calculate the PEC values. The RQ value would likely be lower when metabolism in the target animal, adsorption in the soil, and degradation in the soil, water, and manure environments are considered.

For the first scenario, we considered the potential use of SAFE-GUARD AQUASOL and SAFE-GUARD Type A Medicated Article in the same animals on the same farm. If SAFE-GUARD AQUASOL is approved, it and SAFE-GUARD Type A Medicated Article would be approved for the same indications in swine. It is therefore highly unlikely that both drug products would be used in the same

animals at the same time on the same farm. Thus, there is little or no potential for cumulative exposures to FBZ that are greater than the exposure from the use of SAFE-GUARD Type A Medicated Article alone, which is the drug product with the highest PEC and RQ values.

For the second and third scenarios, we considered the use of multiple FBZ drug products in different species on the same farm and on different farms in the same watershed. The use of SAFE-GUARD Type A Medicated Article in swine will result in the highest PEC_{soil} and PEC_{water} , therefore, the use of this product alone represents the highest risk for environmental impacts. This is true for both a farm scale and a watershed scale type of analysis. For example, if all the animals on a farm or in a watershed were swine that were administered SAFE-GUARD Type A Medicated Article, it would result in the highest surface water concentrations and pose the greatest risk to *D. magna*. However, if there were animal species other than swine that were administered FBZ on the same farm or on different farms in the same watershed, then the concentrations of FBZ entering surface waters would be lower, thereby reducing this risk. The risk would be lower because the FBZ products administered to the different species would result in lower PEC_{soil} and PEC_{water} values than that of SAFE-GUARD Type A Medicated Article for swine. As a result, the RQ of 1.5 for *D. magna* for SAFE-GUARD Type A Medicated Article will be the highest RQ for any type of FBZ exposure, cumulative or otherwise, at either the farm or watershed scale. Based on the conservative assumptions used in calculating the PEC and RQ values, it is concluded that runoff from any combination of approved uses of FBZ will not pose a substantial risk to non-target organisms at a farm scale or within a watershed.

Regulatory Conclusion

Based on the information and analysis described in the EA and FONSI, including risk quotients for sensitive terrestrial and aquatic species, CVM has determined that no significant impacts on the human environment are expected from the proposed use of SAFE-GUARD AQUASOL (fenbendazole suspension for oral suspension) in swine for the proposed indications.

{ see appended electronic signature page }

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Electronic Signature Addendum for Submission ID

Signing Authority (Role)	Letter Date
Steven Vaughn (Office Director)	11/23/2015

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