Registration Decision for the New Active Ingredient Demiditraz for Dog Spot-on Use

September 5, 2013

U.S. Environmental Protection Agency
Office of Pesticide Programs
Registration Division

Registration Decision for the New Active Ingredient Demiditraz, for Spot-on Dog Use for Ticks and Mites

Approved by: _____

Steven Bradbury, Director
Office of Pesticide Programs

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The U.S. Environmental Protection Agency (or the Agency) is granting the first U.S. registrations for pesticide products containing the new active ingredient Demiditraz, (2-[(1S)-1-(2,3-Dimethylphenyl)eythl]-1*H*-imidazole), formulated as a manufacturing-use product and an end-use pet spot-on product for use on dogs only.

Demiditraz is a new acaricide active ingredient developed by Pfizer Animal Health. Demiditraz acts on the octopamine nervous system in acarid invertebrates and acts on neurotransmitter systems, such as the alpha 2 adrenergic receptor, in mammals.

The end use dog spot-on product (EPA Reg. No. 1007-OT, *LA Combo Tick Repellent Combo for Dogs)*, contains two active ingredients: demiditraz (14%) and fipronil (4.8%). The end use product will be used to kill and control blood feeding invertebrates (ticks, fleas, lice and sarcoptic mange mites). Fipronil, as an active ingredient in pet spot-on products, has been previously evaluated by the Agency at a 7.9% concentration, and is not considered a new use for this active ingredient. Therefore, the human health risk assessment only addresses risks from potential exposures to demiditraz. The product is sold in premeasured unit dose vials labeled for application to four dog weight ranges: small, 11 to 20 pounds (lbs); medium, 21 to 33 lbs; intermediate, 34 to 50 lbs; and large, 51 to 66 lbs. It is applied by squeezing the plastic single dose applicator tube to dispense the active ingredient contents onto the skin of the dog. The directions for use instruct the applicator to reapply the product every 30 days. It can be used by homeowners and professional pet care applicators (veterinarians, veterinary assistants, and groomers).

I. HUMAN HEALTH RISK

The following information is a summary of the human health risk from exposure to residues of demiditraz when used as a pet spot-on product applied to dogs.

An evaluation of the toxicity and exposure databases for the new active ingredient, demiditraz, was conducted to assess the human health risk of its use. The database is essentially complete and there are no potential risk estimates of concern for the use of demiditraz. No registered food uses exist for the new active ingredient demiditraz.

A. Toxicological Profile

Demiditraz has a low acute toxicity profile. Demiditraz is classified as Toxicity Category III for acute oral and acute dermal toxicity. A company waiver request was granted for the acute inhalation study with assignment to Toxicity Category IV. Demiditraz is also classified Toxicity Category IV in both acute ocular and acute dermal irritation studies, and is not a dermal sensitizer.

The nervous system is the primary target organ for demiditraz. Pfizer Animal Health reported that demiditraz affects neurotransmitter systems such as the alpha-2 ($\alpha 2$) adrenergic receptor in mammals. Based on behavioral alterations and reduction of body temperature, the primary target of demiditraz in mammals is solely related to its potential effects as an alpha adrenergic receptor agonist as presented by data supporting the mode of action that follows the

International Programme on Chemical Safety (IPCS) framework for establishing a mode of action for a pesticide. Other neurotransmitter systems such as the serotonin system may also be affected.

B. Toxicological Effects and End Points

The nervous system is the primary target organ for demiditraz as indicated by clinical signs of altered function. Evidence of neurotoxicity after demiditraz exposure was throughout the database, but neuropathology was not observed. Altered gait and posture, impaired mobility, decreased rearing, incoordination, lower body temperature, and decreases in motor activity were observed in both sexes in the acute neurotoxicity study (ACN) in rats. Several clinical signs of neurotoxicity, which included subdued appearance, rocks/lurches/sways when walking, hunched posture, hypoactivity, wet and yellow urogenital area, shallow and/or decreased respiration, lacrimation, dilated pupils, and increased/decreased motor activity were observed in both sexes in the subchronic neurotoxicity study (SCN) in rats. Decreased motor activity and altered grooming behavior were observed in both sexes in the 90-day dermal toxicity study in rats. In the developmental toxicity studies, clinical signs suggestive of neurotoxicity were observed in the maternal rats (rocking, lurching, or swaying while walking, piloerection, dilated pupils, and subdued appearance) and rabbits (tremors, prostration, and/or clonic convulsions). In the 2-generation reproduction study in rats, clinical signs (subdued appearance, rocks/lurches/sways while walking, hypoactivity, tremors, clonic convulsions) suggestive of neurotoxicity were observed. In the developmental neurotoxicity study in rats, decreased/increased motor activity and increased startle response amplitude and reduced latency were observed at the high dose where a delay in overall development was observed, mainly in males, as evidenced by decreased body weights throughout lactation in both sexes, and a delay in preputial separation.

The incidental oral endpoint (all durations) for risk assessment was from the oral subchronic neurotoxicity study in the rat with a No Observed Adverse Effects Level (NOAEL) of 5 mg/kg/day. At the study Low Observed Adverse Effects Level (LOAEL) of 25 mg/kg/day, clinical signs of neurotoxicity (subdued appearance, rocks, lurches, or sways when walking, hunched posture, hypoactivity, shallow/decreased respiration, lacrimation, dilated pupil), decreased motor activity, and decreased body weights were observed in both sexes.

The current risk assessment includes a chronic exposure assessment. The Point of Departure (POD) for assessing risks resulting from this duration of exposure was the NOAEL from the subchronic neurotoxicity study. This 90-day duration POD is acceptable for quantifying chronic risks for the long-term incidental oral and inhalation risk assessments because there is no evidence of cumulative toxicity; (i.e., rapid onset (within 30 minutes of exposure) and short duration (2 hours) of transient clinical signs).

No inhalation studies (acute or sub-chronicle) were submitted, but inhalation exposures for all durations are not anticipated from either occupational or residential use of the spot-on product. It should be noted that this study is not relevant to the exposure pattern anticipated for pet use. Further, carcinogenicity studies with demiditraz have not been submitted and are not required for the current non-food/non-feed use.

Dermal endpoints (all durations) for risk assessment were from the route-specific subchronic (90-day) dermal toxicity study in the rat with a LOAEL of 100 mg/kg/day. A NOAEL was not identified. Alterations in motor activity and grooming behavior were observed at all dose levels. The same dermal study and endpoints are appropriate for long-term dermal assessment because there is no evidence of cumulative toxicity.

In the developmental toxicity studies, maternal toxicity was observed in the rat and rabbit, as evidenced by mortality, clinical signs of toxicity, and decreased body weight. Developmental toxicity was observed in the rat and rabbit, as evidenced by decreased fetal body weight and associated delayed ossification of the skeleton in rats and slight increases in the incidence of 27th presacral vertebrae and 13th full ribs in the rabbit. In the rat reproductive toxicity study, mortality, clinical signs, and decreased body weight were observed in parental rats, and decreased survival, decreased brain weight, and decreased pup body weight were observed in the offspring. Reproductive toxicity was not observed.

The mutagenicity/genetic toxicity database consists of a bacterial reverse mutation test (Ames test), a forward mutation test in the V79/HGPRT test, chromosome aberration test in Chinese Hamster Ovary cells, and a mouse bone marrow micro nucleolus test. All studies were determined to be negative for mutagenicity and/or genetic toxicity and there is no concern for mutagenicity/genetic toxicity for demiditraz.

Demiditraz was assessed in a guideline immunotoxicity study and no specific immunotoxicity was identified. No acute or chronic dietary assessments are required since demiditraz is a non-food use pesticide.

C. Food Quality Protection Act

Demiditraz is a non-food/non-feed use chemical with no proposed food uses. As a result, no tolerances have been established for this chemical and the requirements of the Food Quality Protection Act (FQPA) do not apply.

D. Cumulative Effects

Demiditraz is a new chemical with no current registered uses. EPA has not made a common mechanism of toxicity finding. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

E. Residential Exposure and Risk

There is a potential for residential exposures from the use of the demiditraz spot-on for dogs. Short-term residential handler dermal exposure and risk were assessed and are not of concern (i.e., Margin of Exposure (MOEs) are > 300). Inhalation exposures for residential

handler and from post-application exposures to spot-on product are assumed to be negligible. Even so, the inhalation data requirement for the end use product was satisfied using the combined subchronic oral toxicity and neurotoxicity study, and complete adsorption through the respiratory system was assumed.

Residential post-application dermal and incidental oral exposures (all durations) were combined for all children 1 to < 2 years old. Children's combined exposures were presented using the aggregate risk index (ARI) approach. This approach was required to assess combined post-application exposure and risks for children 1 to < 2 years old because the Levels of Concern (LOC) are not the same for dermal and oral routes of exposure (i.e., dermal, 300; and incidental oral, 100), due to the additional uncertainty factor of 3X applied for the lack of a NOAEL in the subchronic dermal toxicity study. For adults, only post-application dermal exposure is anticipated from contact with a demiditraz treated dog.

Pfizer Animal Health submitted a pet residue transfer study in support of demiditraz spot-on use. These data were used in conjunction the Agency's 2012 Residential SOPs to refine the assessment of residential post-application exposures to demiditraz. Day of application (Day 0) residues were used to assess all durations of residential post-application exposure. For the purpose of characterizing longer-term exposures and risks (i.e., intermediate and long-term), multi-day exposure risk estimates were also quantified by use of the average of percent residue using transfer values predicted from Days 0 to 30 (i.e., the proposed product re-treatment interval).

Residential post-application adult dermal, and combined children 1 to < 2 years old exposures are not of concern for all durations of exposure (i.e., adult dermal MOEs are > 300; and children 1 to < 2 years old ARIs are > 1) with use of Day 0 residue data. Exposures estimated for longer-term exposures using 30 day average residue data are approximately 7X below (MOEs 7X greater than) those estimated for all durations using Day 0 data.

F. Occupational Exposure and Risk

The Agency uses the term "handlers" to describe those individuals who are involved in the pesticide application process. The anticipated use patterns and current labeling indicate occupational exposure scenarios based on the types of equipment and techniques that can potentially be used for demiditraz applications.

Occupational exposures to veterinarians, veterinary assistants, and groomers may occur from the application of the proposed spot-on product to dogs. Dermal exposure assessments (all durations) were conducted to assess occupational handlers applying the demiditraz spot-on to dogs. Occupational handlers of the product could potentially treat up to 170 dogs per day without resulting in risks of concern for all durations assessed (i.e., MOEs are ≥ 300); a single handler treating more than 170 dogs per day is unlikely; therefore, no risk concern exists for this scenario.

Occupational handler inhalation exposure is expected to be negligible and was not quantitatively assessed. Furthermore, a quantitative assessment of occupational post-application

exposure from demiditraz spot-on product was not conducted. Occupational post-application activities are expected to be significantly less than residential post-application exposures, because dogs are expected to be treated and returned to their owners such that post-application contact will be negligible.

G. Aggregate Dietary (Food + Drinking Water) Risk

Demiditraz currently has no registered food/feed uses and no drinking water residues are expected to result from pet use; therefore, aggregate exposure includes only the exposure from the dog spot-on use.

H. Product Specific Acute Toxicity and Companion Animal Safety

The registrant submitted five studies encompassing an acute oral, acute dermal, primary skin irritation, primary eye irritation, and dermal sensitization studies to satisfy the acute toxicity data requirements associated with the use of the formulated end use product. All of these submitted acute studies were found to be acceptable. A waiver for the acute inhalation data requirements was submitted and found to be acceptable due to the fact that the product, as packaged and formulated, has very little volatility, is packaged in small containers, and is designed to adhere to the skin of the animal, thereby severely limiting the potential for acute inhalation exposure to the end use product.

In a 28-day companion animal safety study, treatment-related effects were limited to transient minimal skin irritation (without erythema or other skin changes), scratching at the dose site, and matted hair at the dose site, which resolved within two days of dosing. There were no treatment-related effects on mortality, body weight, food consumption, hematology, or clinical chemistry parameters. Additionally, a 5X (five times) margin of safety has been determined from the study wherein approximately 8 week-old juvenile beagle dogs were administered the proposed combined demiditraz/fipronil formulations at five times the maximum recommended dosing volume on the label of 0.2 mL/kg. Therefore, the companion animal safety study was found to be acceptable with limitations of the use of the product only to dogs older than 9 weeks of age and no less than 11 pounds, based upon and commensurate with the age and size of the animals treated in the study.

II. Ecological and Environmental Risks

An environmental and ecological risk assessment is not relevant for the demiditraz pet spot- on use since environmental exposure for this use is expected to be negligible. The total amount of demiditraz for the largest dog (weighing from 51 to 66 lbs) pet spot-on dose is 1.3 x 10^{-3} lbs. of demiditraz or 600 mg. Demiditraz, as formulated into a pet spot-on product, adheres to the animal's fur and skin and therefore not expected to get into the environment.

III. Consideration of Environmental Justice

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To help address potential environmental justice issues, the Agency sought public comments from any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to demiditraz as compared to the general population.

IV. REGULATORY DECISION

As required by FIFRA, the Agency published a notice in the Federal Register of February 9, 2010 announcing receipt of applications from Pfizer Animal Health to register the active ingredient demiditraz for indoor, non-food, companion animal spot-on products (one manufacturing use and one end use product). No comments were received in response to the notice of receipt.

Prior to this final decision document, the Agency posted on its website a proposed decision document on July 23, 2013 and provided a 30 day comment period for the public. No comments were received on the proposed decision document.

The Agency is unconditionally registering the new active ingredient demiditraz, formulated as a manufacturing use product under section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). This product will be formulated into products for the following use: indoor, non-food, companion animal spot-on.

A. Data Requirements

The database of toxicology studies available for demiditraz provides an adequate characterization of the human hazard and exposure. There are no outstanding studies for this proposed indoor nonfood use for demeditraz. Based upon the Agency's assessment, it has been determined that there are no risks of concern for the proposed use of demiditraz for use on pets as a spot on application.

B. Required Label Changes

No label changes are required.

C. Agency's Decision

The Agency concludes that: 1) the applicant has submitted satisfactory data to support the unconditional registration under the Federal Fungicide and Rodenticide Act (FIFRA) Section 3(c)(5) of the new active ingredient, demiditraz, as a spot-on liquid product for dogs to control ticks and mites, 2) the use would not cause any unreasonable adverse effect on human health or the environment. Therefore, the Agency is granting this unconditional registration.