

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205003Orig1s000**

**ENVIRONMENTAL ASSESSMENT**



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmaceutical Science/Immediate Office**

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**Memorandum**

**Date:** September 30, 2014

**From:** James P. Laurenson, OPS/ONDQA/EA Staff

**To:** Yvonne Knight, ONDQA PM  
Kasturi Srinivasachar, ONDQA CMC Lead  
Charles Jewell, ONDQA CMC Primary Reviewer

**Subject:** NDA 205-003, Prestalia (Perindopril Arginine/Amlodipine Besylate) Tablets; Review of Claim for Categorical Exclusion

**Sponsor:** Symplmed Pharmaceuticals, LLC (Symplmed)

**A. Summary**

Symplmed has submitted a new drug application (NDA) for Prestalia, a fixed-dose combination of perindopril arginine (perindopril) combined with amlodipine besilate (amlodipine). This product uses tablets for oral administration. The sponsor submitted an environmental assessment (EA) that includes a claim for categorical exclusion from an EA under 21 CFR 25.31(b). FDA reviewed the submitted and other information and has concluded that the categorical exclusion request is adequate. There is no information available indicating that additional environmental information is warranted for this application. The claim of categorical exclusion is accepted.

**B. Background**

Symplmed has filed an NDA pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act (FFDCA) for Prestalia, a fixed-dose combination of perindopril and amlodipine. Perindoprilat is the primary entity of interest released into the environment through use of the pro-drug perindopril, and thus perindoprilat is the focus of this review.

An EA dated February 18, 2014 was submitted to FDA pursuant to 21 CFR Part 25. The EA contains a claim for categorical exclusion from an EA under 21 CFR 25.31(b), which is for actions that increase the use of the active moiety but for which the estimated concentration of

the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). The sponsor subsequently submitted, on September 18, 2014, the required statement that to the sponsor's knowledge, no extraordinary circumstances exist.

### C. Review of Claim for Categorical Exclusion

The EA provided estimated introductory concentrations (EICs) for the two active ingredients of interest, (b) (4) ppb for amlodipine and (b) (4) ppb for perindoprilat, which are both less than the 1 ppb categorical exclusion value. These concentrations correspond to use amounts of (b) (4) respectively. The calculations used by the sponsor are correct, and thus assuming the use amounts are accurate, the EICs are indeed less than 1 ppb, which satisfies the categorical exclusion criteria for 21 CFR 25.31(b).

The statement regarding "no extraordinary circumstances" also was considered. FDA examined the EA and additional literature information for this purpose. Specifically, the sponsor provided an EA that includes calculated assessment factors (AFs) that exceed the Tier 1 AF of 1,000 noted in FDA guidance (USFDA 1998). The sponsor states that these results indicate that amlodipine and perindoprilat are not expected to be toxic to aquatic organisms at the Maximum Expected Environmental Concentration (MEEC). However, the sponsor used chronic ecotoxicity values for their calculate AF, while the FDA guidance recommends acute values for Tier 1. This use of chronic values resulted in calculated AFs that likely are much lower than what would have resulted had acute values been used. That is, the use of acute values likely would have resulted in calculated AFs that would have exceeded the Tier 1 AF of 1,000 by an even larger amount. Therefore, based on these data, FDA would agree that these results indicate that amlodipine and perindoprilat are not expected to be toxic to aquatic organisms at the MEEC.

The data provided in the EA also could be used to calculate risk quotients (RQs) of the predicted environmental concentration (PEC) divided by the predicted no-effects concentration (PNEC). While a detailed development and review of PEC/PNEC ratios is beyond the scope of this categorical exclusion review, it is clear from the AFs that these ratios would be substantially less than 1, even with several worst-case assumptions. Nevertheless, FDA conducted a limited literature search on amlodipine and perindoprilat.

In one finding for amlodipine, 10 ppb inhibited the ability of dissected polyps from the invertebrate (cnidarian) *Hydra vulgaris* to regenerate a hypostome, tentacles, and foot (Pascoe et al. 2002). In another, a photoderivative of amlodipine, noted as more toxic than amlodipine, resulted in a chronic toxicity EC50 of 41 ppb for population growth inhibition in the crustacean *Ceriodaphnia dubia* (DellaGreca et al. 2007). These values are 50 and 200 times the MEEC noted above for amlodipine. While neither ecotoxicity value is a preferred no-observed-effect concentration (NOEC), these values also are associated with unconventional endpoints and testing methods that do not necessarily indicated adverse population impacts. Furthermore, the highly conservative nature of the MEEC indicates that the ratios would be significantly higher if PECs were used as the denominator. One study did describe a provisional PNEC for amlodipine of 0.28 ppb (Roos et al. 2012). This value is

also higher than the MEEC noted above, and thus would be higher than the PEC. No additional data could be found for perindopril or perindoprilat.

In response to recent research that indicates that drugs with hormonal activity, and in particular drugs that interact with estrogenic, androgenic, or thyroid (E, A, or T) hormone pathways, have the potential for adverse effects when present in the environment at concentrations that are normally subject to a categorical exclusion, the potential for amlodipine and perindoprilat to interact with E, A, or T pathways was examined. The nonclinical review (USFDA 2014) was examined and found to contain no indications of reproductive and developmental toxicology. Thus, no significant E, A, or T risk is expected from this specific application.

Next, cumulative risk was examined by combining the use amount estimates from this application with the current use amounts for the active ingredients. The 2013 sales amounts for amlodipine and perindopril are (b) (4). This application likely would result in some replacement of these amounts, but using the “worst-case” assumption that this application would only add to existing use amounts, the new amounts resulting from approval of this application would be (b) (4).

For both ingredients, the EICs (MEECs) would still be (b) (4) (b) (4)

Thus, there is little available data to establish that, at the expected level of exposure, there is the potential for serious harm to the environment from this action, and thus the statement regarding no extraordinary circumstances appears to be reasonable.

#### D. Conclusion

FDA concludes that the categorical exclusion request, supplemented by information submitted in an EA, which aids in determining whether extraordinary circumstances exist, is adequate. There is no information available indicating that additional environmental information is warranted in order to evaluate the claim of categorical exclusion. The claim of categorical exclusion is accepted.

#### E. References

DellaGreca M, Iesce MR, Isidori M, Montanaro S, Previtiera L, and Rubino M. 2007. Phototransformation of amlodipine in aqueous solution: toxicity of the drug and its photoproduct on aquatic organisms. *International Journal of Photoenergy*. Article ID 63459.

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Roos V, Gunnarsson L, Fick J, Larsson DGJ, and Rudén C. 2012. Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first-tier selection. *Science of the Total Environment*. 421, 102-110.

USFDA. 1998. *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application.*

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/s/  
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09/30/2014