

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: November 24, 2004

From: Kathy M. Robie-Suh, M.D., Ph.D.
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Subject: NDA 20-333, Agrylin (anagrelide hydrochloride)
Pediatric Supplement (SE5-008), submitted 03/12/04
Labeling Supplement (SLR-009), submitted 03/12/04
Major amendment to SE5-008 submitted September 8, 2004

To: NDA 20-333

Agrylin (anagrelide hydrochloride) is an orally active agent approved for treatment of patients with thrombocythemia, secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-hemorrhagic events. The sponsor has conducted a study in pediatric patients in response to a Written Request from the agency. The reports were submitted as a pediatric efficacy supplement (SE5-008) on March 12, 2004 and additional information was sent May 11, 2004. Combined with that submission was a labeling supplement (SLR-009) proposing changes to the **PRECAUTIONS, Drug Interactions** portion of the labeling based on two anagrelide drug-drug interaction studies of coadministration of single doses of anagrelide and warfarin and coadministration of single doses of anagrelide and digoxin.

These submissions were reviewed by Chemistry, Clinical Pharmacology and Biopharmaceutics, Clinical, and Pharmacology and Toxicology. A recommendation was made for approval of the both supplements with recommendations for labeling revisions. (See my Medical Team Leader memorandum for this submission, completed 9/8/04, signed 9/9/04). The labeling revisions were discussed with the sponsor and revised labeling was submitted on September 8, 2004. On September 8, 2004 the sponsor also submitted a major amendment to the pediatric supplement (SE5-008). On September 9, 2004 the division issued an action letter indicating that SLR-009 was approvable pending approval of SE5-008. The review clock for supplement SE5-008 was extended to allow for review of the additional information (see extension letter dated 9/10/04).

Clinical:

The major amendment submission to SE5-008 contains a re-issued clinical study report for the pediatric study (SPD422-202), re-categorized race and ethnicity data, and a post-marketing safety summary in pediatric patients. This new material was reviewed by the

medical reviewer (Dr. Min Lu, 10/26/04). The new material identified three new serious adverse events in pediatric patients from the post-marketing safety database: anemia, cutaneous photosensitivity and elevated leukocyte count. There were no significant changes in the study report for SPD422-202. The Medical Officer's Review recommends addition of the following sentence to the last paragraph in the **PRECAUTIONS, Pediatric Use** section of the labeling: "Other adverse events reported in spontaneous reports and literature reviews include anemia, cutaneous photosensitivity and elevated leukocyte count." The clinical review does not recommend any labeling changes for the pediatric study beyond those made in the previous Medical Officer's Review (8/20/04).

Other Information:

Included in the proposed labeling for SE5-008 and SLR-009 were additional changes in the **CLINICAL PHARMACOLOGY** section regarding metabolism of anagrelide and identifying 3-hydroxy anagrelide as an active metabolite of anagrelide. Also, in the **PRECAUTIONS, Drug Interactions** subsection additional information regarding the metabolism of anagrelide was added.

The data to support including this additional information in the labeling were reviewed by Pharmacology (Dr. R. Honchel, 11/5/04) and Clinical Pharmacology and Biopharmaceutics (Dr. T.-M. Chen, 11/12/04) in the course of evaluating information to address a Citizen Petition (2004P-0365/CP1 and PSA1) from Shire US, Inc. for Agrylin (anagrelide hydrochloride). Information in the material submitted in support of the Citizen Petition also asserted that "the metabolite [3-hydroxy anagrelide] was equipotent with the parent molecule in its potential platelet lowering activity, and was forty times more potent as a phosphodiesterase III (PDE III) inhibitor and, thus, as a cardioactive agent." (8/13/04 submission). The petition also asserted a differential effect of food intake on the parent compound and the 3-hydroxy metabolite. Pharmacology review concluded that "the sponsor has not conclusively shown that 3-OH anagrelide is an active metabolite of anagrelide. 3-OH anagrelide did produce cardiostimulant effects in a dog. These effects were not different than the effects produced by anagrelide in several species." Clinical Pharmacology and Biopharmaceutics review (Dr. T.-M. Chen, 11/12/04) found that the sponsor's attempts to correlate anagrelide and 3-hydroxy anagrelide c_{max} values separately with maximal change in heart rate and anagrelide and 3-hydroxy anagrelide AUC values separately with individual platelet count changes at steady state from baseline in the pediatric study were "too simplistic to show that 3-hydroxy anagrelide is pharmacologically active." Also, the review noted that "There is no *in vivo* data in humans where 3-hydroxy anagrelide was administered and its pharmacologic activity with respect to platelet count reduction or cardiovascular activity was ascertained."

With regard to the labeling, Clinical Pharmacology and Biopharmaceutics additionally recommended (Dr. T.-M. Chen, 11/23/04) that information regarding the metabolites beginning with sentence eleven under the **CLINICAL PHARMACOLOGY** section should read: "Two major metabolites have been identified (RL603 and 3-hydroxy anagrelide). There were no apparent differences between patient groups for t_{max} and $t_{1/2}$ for anagrelide, 3-hydroxyanagrelide, or RL603." Also, the review recommended that in

the last paragraph of the **CLINICAL PHARMACOLOGY** section of the labeling beginning with : “(b) (4) to the end of the paragraph should be deleted. Since the Pharmacology review and the Clinical Pharmacology and Biopharmaceutics review have not concluded that 3-hydroxy anagrelide is demonstrated to be an active metabolite of anagrelide, these sentences could be misleading as they imply that there has been demonstration of pharmacodynamic importance of the 3-hydroxy metabolite. Because the statement “ (b) (4) could be interpreted to mean that the clinical importance of this metabolite has been demonstrated, this sentence also should be deleted (discussed with Dr. T.-M. Chen, 11/23/04).

(b) (4)

Conclusions and Recommendations:

Supplements SE5-008 and SLR-009 should be approved with the labeling that was faxed to the sponsor on 9/2/04 revised further as follows:

1. Sentences eleven and twelve under the **CLINICAL PHARMACOLOGY** section should read: “Two major metabolites have been identified (RL603 and 3-hydroxy anagrelide). There were no apparent differences between patient groups for t_{max} and $t_{1/2}$ for anagrelide, 3-hydroxy anagrelide, or RL603.” The section should continue with the sentence beginning: “When a 0.5 mg dose of anagrelide...”
2. The sentences in the last paragraph of the **CLINICAL PHARMACOLOGY** section of the labeling beginning with: “ (b) (4) (b) (4)” to the end of the paragraph should be deleted.
3. At the end of the last paragraph in the **PRECAUTIONS, Pediatric Use** subsection of the labeling add the following sentence: “Other adverse events reported in pediatric patients in spontaneous reports and literature reviews include anemia, cutaneous photosensitivity and elevated leukocyte count.”

cc:

NDA 20-333
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/s/

Kathy Robie-Suh
11/24/04 10:19:18 AM
MEDICAL OFFICER