DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-333
IND (b) (4)

Shire Pharmaceutical Development, Inc.
Attention: Amy Butscher, M.S.
Manager, Regulatory Affairs
1801 Research Blvd., Suite 600
Rockville, MD 20850

Dear Ms. Butscher:

Please refer to your correspondence dated April 29, 2003, requesting changes to FDA's March 27, 2003, Written Request for pediatric studies for Agrylin (anagrelide HCl) Capsules.

We reviewed your proposed changes and are amending the Written Request. A corresponding advice letter will also be sent that addresses additional recommendations concerning the April 29, 2003 submission.

The "**Entry Criteria"** section has been revised as follows:

> "Patients must have a documented history of thrombocythemia secondary to myeloproliferative disorders (e.g., essential thrombocythemia, polycythemia vera, and/or other myeloproliferative disorders). ~~Patients entering the study already on anagrelide must have received anagrelide therapy for at least the past two months, with a stable maintenance dose of anagrelide for at least one month prior to study enrollment and platelet count of < 600,000/µL.~~"

For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Request dated March 27, 2003.

To obtain needed pediatric information on anagrelide, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following study:

- **Type of study:**

  A safety, pharmacokinetic (PK), and pharmacodynamic (PD) study in pediatric patients with thrombocythemia secondary to myeloproliferative disorders who are currently stabilized on anagrelide treatment or who are newly diagnosed with thrombocythemia secondary to myeloproliferative disorders requiring treatment. Review of prior anagrelide use (including doses and duration of use), starting study doses, the extent of dose adjustments, resulting platelet counts and adverse events will also be included in the study. You are encouraged to include a concurrent adult study arm to allow a comparison of safety and PK data.

- **Objective(s) of the study:**

  1) To assess the safety and tolerability of anagrelide in pediatric/adolescent (<16 years old) patients with thrombocythemia secondary to myeloproliferative disorders (MPDs)
  2) To evaluate the steady-state pharmacokinetics of anagrelide and, where possible, its metabolite(s)
  3) To collect anagrelide dosing information, including data on starting dose of anagrelide, dose adjustments, and platelet counts in these patient populations for PD assessments
  4) If possible, to evaluate the correlation, if any, between anagrelide daily dose, resultant anagrelide plasma concentrations and platelet counts

- **Indication to be studied**

  Treatment of thrombocythemia secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms, including thrombotic and hemorrhagic events

- **Age group in which studies will be performed:**

  Two age groups: adolescents ≥ 12 to < 16 years old; pediatric patients < 12 years old

- **Entry Criteria:**

  Patients must have a documented history of thrombocythemia secondary to myeloproliferative disorders (e.g., essential thrombocythemia, polycythemia vera, and/or other myeloproliferative disorder).

- **Number of patients to be studied:**

  For patients ≥ 12 to < 16 years old: A minimum of 10 patients will have baseline assessments done, receive study drug for at least 1 month on study, have PK and PD data collected, have safety data collected, and have follow-up assessments after 1 month of treatment on study. A minimum of 6 patients will have follow-up assessments and safety information collected after at least 3 months of treatment on study.

  For pediatric patients < 12 years old: A minimum of 8 patients will have baseline assessments done, receive study drug for at least 1 month on study, have PK and PD data collected, have safety data collected, and have follow-up assessments after 1 month of treatment on study. A minimum of 5 patients will have follow-up assessments and safety information collected after at least 3 months of treatment on study.

  The above sample size estimates for the PK studies are based on traditional PK study designs and more patients will be needed for a population pharmacokinetics approach.

- **Study Endpoints:**

  Pharmacokinetic endpoints will include:

  Descriptive pharmacokinetic parameters (e.g., steady-state C_{max}, T_{max}, C_{min}, $AUC_{0-\tau}$, apparent oral clearance, and $T_{1/2}$)

  Pharmacodynamic endpoints will include:

  Platelet counts
  Change in platelet counts
  Dose adjustments

  Safety endpoints will include:

  Thrombotic and hemorrhagic events
  Symptoms of thrombocythemia
  Adverse Events (AEs), including but not limited to palpitations, hypotension, hypertension, vasodilation, tachycardia, congestive heart failure, and renal failure
  Clinical laboratory studies, including CBC with platelet counts, serum creatinine, hepatic transaminases (ALT, AST)
  Cardiac function as assessed by cardiac ECHO and ECG
  Patient medical history, including information to support diagnosis, platelet counts and any history of thrombotic or hemorrhagic episodes
  Where patients enter the study already on anagrelide, safety information from patient medical charts should include starting dose and dose adjustment information and any clinical or laboratory adverse experiences during anagrelide therapy.

- **Drug Information:**

  Dosage form: Agrylin® 0.5 mg and 1.0 mg capsules or other age-appropriate formulation.

  Route of Administration: Oral. Dosing time as related to food intake should be consistent and documented.

  Regimens: As prescribed by patient's physician. Initial anagrelide dose and changes in doses will be documented.

  Develop age-appropriate formulation(s) of anagrelide. The relative bioavailability of these age-appropriate formulations, as compared to marketed formulations of Agrylin® Capsules (0.5 mg, 1.0 mg) should be determined. The full study reports of these relative bioavailability studies should be submitted to the Agency. If age-appropriate formulation(s) can not be developed, you will need to provide complete documentation of your attempts, along with justification as to why this was not possible, as part of your letter requesting an amendment to this Written Request. Marketed formulations of Agrylin® Capsules (0.5 mg, 1.0 mg) may be administered to pediatric patients who are able to swallow them.

- **Drug specific safety concerns:**

  Cardiovascular effects: Cardiovascular effect of anagrelide will be monitored closely by a 24-hour ambulatory ECG monitoring. Baseline and end-of-the study 12-lead ECG's also will be included. Cardiac ECHO will be performed at study entry, at 3 months on study for patients with 3-month follow-up, and at 6 months on study, where possible. Patients will be monitored for cardiovascular symptoms, including palpitations, hypotension, hypertension, congestive heart failure symptoms, tachycardia and vasodilation.

  Renal function: Renal function will be assessed at study entry and followed during the study using serum creatinine, BUN and urinalysis.

  Hepatic function: Hepatic transaminases and serum bilirubin will be assessed at study entry and followed during the study.

  Platelet counts: Platelet counts will be followed during the study. Patients will be monitored for bleeding events.

- **Statistical information, including power of study and statistical assessments:**

  Pharmacokinetic results will be summarized using descriptive statistics. Clinical laboratory data and adverse event data will be summarized using descriptive statistics. Where possible, attempt will be made to evaluate relationship between anagrelide daily dose, anagrelide plasma concentrations and platelet counts.

- **Labeling that may result from the studies:**

  Appropriate sections of the label may be changed to incorporate the findings of the studies.

- **Format of reports to be submitted:**

  Full study reports must be submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

- **Timeframe for submitting reports of the studies:**

  Reports of the above studies must be submitted to the Agency on or before March 13, 2004. Please keep in mind that pediatric exclusivity only attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

- **Response to Written Request:**

  As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a **new drug application (NDA) or as a supplement to an approved NDA** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Ryan Barraco, Consumer Safety Officer, at 301-827-0191.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Beitz
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