Clinical Review for NDA 20-333/SE5-008

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, Agrylin is approvable for the treatment of 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 in pediatric patients.

One safety, pharmacokinetic (PK) and pharmcodynamic (PD) study was conducted in 17 pediatric patients 7 to 14 years of age as compared to 18 adult/adolescent patients 16 to 86 years of age with established diagnosis of thrombocythemia secondary to myoproliferative disorders. The study showed similar frequency and types of adverse events in pediatric patients as compared to adult patients.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no new recommendations on Phase 4 study. Risk management includes that the sponsor should revise labeling as recommended (See appendix).

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Product name: Agrylin

Drug class: Platelet-reducing agent

In response to the Written Request, one safety and PK/PD study (SPD422-202) was conducted in 17 pediatric patients 7 to 14 years of age as compared to adult/adolescent patients 16 to 86 years of age with established thrombocythemia secondary to myoproliferative disorders.

B. Efficacy

Efficacy was not evaluated in the study. Myeloproliferative disorders in children is very rare (annual incidence of 0.7-0.8 per million) based on a literature report (Hasle, et al., British J. of

Hematology 1999; 107:1027-32). It is generally considered that the course of the disease in adult and pediatric populations is similar for myeloproliferative disorders (with exceptions noted in asymptomatic pediatric patients or those presenting with familial thrombocytosis). The frequency of symptoms and complications of thrombocythemia, secondary to myeloproliferative disorders in pediatric patients is comparable to that found in adult patients (Dror, British J. of Hematology 1999; 107:691-8). Anagrelide has been shown to reduce the thrombotic/hemorrhagic complications in pediatric patients by decreasing the platelet counts in previous compassionate use study (included in current labeling in Pediatric Use section under Precautions) and case reports from literature (Lackner H, et al., J. Pediatr Hematol Oncol 1998, 20:469-73; Chintagumpala MM, et al., Am J Pediatr Hematol Oncol 1991, 13:52-6).

C. Safety

One study (SPD422-202) was conducted in pediatric patients 7-14 years of age as compared to adult/adolescent patients 16 to 86 years of age with established thrombocythemia secondary to myoproliferative disorders.

Study SPD422-202 was a multicenter, safety, pharmacokinetic and pharmcodynamic study in pediatric patients as compared to adult/adolescent patients. A total of 17 pediatric patients and 18 adult/adolescent patients were enrolled from 17 centers in 9 countries. Pediatric patients ranged in age from 7 to 14 years (mean age of 11 years) and no children were under 7 years of age due to scarcity of patients in this age range. There were 8 patients 7-11 years of age and 9 patients 12-15 years of age. In adult/adolescent group, one patient was under 18 years (at 16 years) of age and most of patients were 50 years or older (mean age of 63 years). There was a similar distribution of gender in pediatric patients (8 males and 9 females) and adult/adolescent patients (9 each for males and females). The majority of patients were Caucasian (65% in pediatric patients and 89% in adult/adolescent patients). The primary diagnosis for all pediatric patients was essential thrombocythemia (ET). For adult patients, most frequent diagnosis was ET (82.9%) followed by polycythemia vera (PV) (14.3%). The mean duration from disease diagnosis to study entry was 3.6 years in the pediatric group and 4.9 years in the adult group.

At study entry, most pediatric patients (94%) and adult/adolescent patients (72%) had prior anagrelide exposure. In the pediatric group, one (5.9%) patient was anagrelide naïve, 3 (17.6%) patients were on anagrelide titration, and 13 (76.5%) were on maintenance at study entry. In the adult/adolescent group, 5 (27.8%) patients were anagrelide naive, 3 (16.7%) patients were on anagrelide titration, and 10 (55.6%) patients were on anagrelide maintenance at study entry. The duration of prior anagrelide exposure was similar between the two groups with a mean of 811.8 days for the pediatric group and 798.4 days for the adult group. The mean duration of exposure on the study was also similar for the pediatric (92.5 days) and adult (90.5 days) groups. All patients received anagrelide for ≥85 days on the study. Mean overall anagrelide exposure at any dose level was 759.1 days for all enrolled patients, 856.5 days for the pediatric group and 667.1 days for the adult group.

For patients who were anagrelide naïve, the starting dose of anagrelide was 0.5 mg once daily for both pediatric (one patient) and adult patients (5 patients). For patients who had prior anagrelide

exposure, the starting dose, based on retrospective review, was 1mg total daily dose in most pediatric and adult/adolescent patients with a range of 0.75mg to 1.5 mg total daily dose in pediatric patients and 0.5 mg to 2.0 mg total daily dose for adult/adolescent patients. The median final doses for each of the pediatric (≤ 11 years old), adolescent (12-15 years old) and adult (≥16 years old) age groups were 1.25 mg (range 1.0 mg - 4.5 mg), 2.0 mg (range 1.0 mg - 6.0mg) and 1.5 mg (range 0.5 mg - 7.0 mg), respectively.

In the study, 21 patients (60.0%) reported 54 AEs. The incidence of AEs for patients in the pediatric group (52.9%, 9/17) was slightly lower than for patients in the adult group (66.7%, 12/18). Adverse events that were reported by all patients at an incidence rate > 5% (2 or more patients) were palpitation, fatigue, fever, dizziness, headache, epistaxis, and urinary incontinence. The study results showed more pediatric patients than adult patients experienced fever (11.8% vs. 0%), epistaxis (11.8% vs. 0%), and headache (11.8% vs. 5.6%) and more adult patients than pediatric patients experienced palpitations (16.7% vs. 0%), dizziness (11.1% vs. 0%), and urinary incontinence (11.1% vs. 0%), and fatigue (11.1% vs. 5.9%). The difference in the types of adverse events observed between the pediatric and adult patients in the study may partially due to the limited number of patients available in the study.

Three patients (17.6%) in the pediatric group reported 8 AEs deemed possibly or probably related to study drug by Investigators as compared to 6 adult patients (33.3%) who reported 14 AEs possibly or probably related to study drug. These AEs were fever, anemia, peripheral edema, and epistaxis in pediatric group only, palpitation, angina pectoris, diarrhea, dizziness, anxiety, dyspnea, and pruritis in adults only, and fatigue and headache in both groups.

There were no deaths reported in the study. One subject (2.9%, 1/35) reported a serious AE during the study (inhalation of gases from lighter). This event was not considered to be related to anagrelide treatment by investigator. No subject was withdrawn from the study because of an AE.

Among the 29 patients who had prior anagrelide exposure, 15 patients (51.7%) reported 61 AEs based on retrospective review of patients' records. The incidence of AEs for patients in the pediatric group (50%, 8/16) was similar to the patients in the adult group (53.8%; 7/13). Nine of 29 (31%) patients reported AEs deemed related to study drug by Investigators. The incidence of related AEs for patients in the pediatric group (31.3%; 5/16) was similar to that for patients in the adult group (30.8%; 4/13). The type of events reported as related to study drug were similar between the pediatric (palpitations, headache, nausea, vomiting, abdominal pain, back pain, anorexia, fatigue and muscle cramps) and adult (tachycardia, palpitations, headache, dizziness, dyspnea, nausea, abdominal pain, diarrhea, edema peripheral and vascular skin condition) groups. The numbers of related events were also similar between the pediatric group (40.5%; 15/37) and the adult group (45.8%; 11/24). One (6.3%; 1/16) SAE (tooth abscess) was reported in a 12-year old female who was on a total daily anagrelide dose of 4.5mg. This event was not considered to be related to anagrelide by investigator and did not lead to discontinuation of therapy. One adult patient (7.7%, 1/ 13), a 79-year old female receiving a total daily anagrelide dose of 2 mg, experienced four AEs (palpitations, peripheral edema, dizziness and dyspnea) that

led to discontinuation of anagrelide. Events resolved upon discontinuation of anagrelide therapy. Anagrelide was reinstituted six months later at a reduced dosage (total daily dose of 1.5 mg).

In the study, 6 patients (2 pediatric and 4 adult patients) demonstrated changes in the ECG from baseline. These included one anagrelide naive adult patient (an 84-year old female with an on-study-drug exposure of 14 weeks), and 2 pediatric and 3 adult patients who were on anagrelide maintenance therapy at study entry (overall anagrelide exposure ranging from 92 weeks to 294 weeks). The reported EGG changes in pediatric patients were sinus arrhythmia in a 7-year-old male on anagrelide for 92 weeks, and incomplete right bundle branch block in a 14-years-old male on anagrelide for 135 weeks. The ECG changes in adult patients were ST/T changes (a 84-year-old female anagrelide naïve patient with history of hypertension and a 68-year-old female on anagrelide 109 weeks with history of hypertension), T wave inversion (a 30-year-old male on anagrelide for 294 weeks), and long P-R interval but normal P-R interval (a 79-year-old female on anagrelide for 112 weeks with history of hypertension). These ECG changes were not considered to be clinically significant by the investigators.

Ambulatory 24 hour ECG monitoring showed the mean heart rate increased 12.5 bpm from baseline in pediatric patients who were anagrelide naïve or on dose titration at study entry as compared to 3.4 bpm in adult patients who were anagrelide naïve or on dose titration at study entry. However, numbers of these patients were very small. Superventricular and ventricular premature beats were recorded more in adult patients than pediatric patients, most as single beat. One pediatric patient, a 10-year-old male with an overall anagrelide exposure of 217 weeks, and two adult patients, a 79-year-old female with known hypertension and transient ischemic attacks who has overall anagrelide exposure of 112 weeks and an 83-year-old-male who was anagrelide naive at study entry with on study exposure of 13 weeks, were found to have short 3 to 4 beat asymptomatic runs of ventricular tachycardia. These finding were not considered to be related to study treatment by investigator.

There were 3 pediatric patients who had abnormal echocardiogram at study entry (atrial septal defect, faint mitral regurgitation, and unspecified changes). No new changes from screening were noted at the end of the study (Day 90) for any pediatric patients. There were three adult patients (a 71- year old female, a 71-year old male, and a 55-year old male; with overall anagrelide exposure of 90 weeks, 257 weeks and 84 weeks, respectively) who reported new abnormalities from baseline. These abnormalities were minor valvular insufficiency in the first two patients and the mild left ventricular regurgitation in the third patient. These changes were considered to be related to patients' underlying cardiac conditions by investigators. No significant changes from baseline in ejection fraction were reported at 1-month and 3-months on the study in anagrelide naïve patients (one pediatric and 5 adult patients) or in any patients who were already on anagrelide at study entry (16 pediatric and 13 adult patients).

Three pediatric patients experienced at least a single episode of elevated pulse rate (above a defined normal range of 65-120 bpm) during the Day 30 pharmacokinetic period compared with one adult subject. No elevations in pulse rate were observed during the Day 90 assessment period. Four pediatric patients experienced at least a single episode of reduced systolic or diastolic blood pressure (below the normal range of 90-180 mmHg or 40-100 mmHg,

respectively) during the Day 1 or Day 30 assessments as compared to no similar events in the adult subject group. Of these observed events, one pediatric subject, an 11 year old male with ET, experienced a concomitant reduction in either systolic or diastolic blood pressure and an increase in heart rate. Although out of normal range, none of these patients reported episodes of dizziness or palpitations. These events were not considered to be clinically significant by investigator.

In conclusion, Study SPD422-202 showed the similar frequency of adverse events during the study between pediatric patients and adult patients. The most common adverse events were fever, epistaxis, headache and fatigue in pediatric patients, and palpitation, dizziness, urinary incontinence, fatigue, and headache in adult patients. The types of drug-related adverse events were similar between pediatric and adult patients based on retrospective review of patients' records. These adverse events included palpitations, headache, nausea, vomiting, abdominal pain, diarrhea, dizziness, back pain, dyspnea, anorexia, fatigue and muscle cramps, peripheral edema and vascular skin condition. The safety results were limited by the number of patients available in the study and most study patients who were already on anagrelide maintenance at study entry.

D. Dosing

There were limited clinical data available in the study to make the starting dose recommendation for pediatric patients because the majority of pediatric patients were already on anagrelide treatment at study entry (an average of 2 years). In the retrospective review of patients' records in the study, the total daily starting dose appeared to be lower (0.75 mg to 1.5 mg per day) in pediatric patients, as well as in adult patients (0.5 mg to 2.0 mg per day), than current recommended starting dose (2 mg per day as given by 0.5 mg qid or 1 mg bid) for adult patients. However, the study was limited by the number of patients available and a retrospective review of data for starting doses.

E. Special Populations

Gender

There were 8 males and 9 females in the pediatric group and 9 males and females each in the adult/adolescent group in the study. No significant gender effect on safety was observed in the trial.

Age

There were 8 patients 7 to 11 years of age and 9 patients 12 to 15 years of age in the pediatric group. There was one patient at 16 years of age and 17 patients older than 18 years in the adult group. No patient younger than 7 years of age was enrolled. No significant age effect on safety was observed in the trial.

Race

There were 11 Caucasian, 3 Black, and 3 Asian pediatric patients, and 16 Caucasian, 1 Black, and 1 Hispanic adult/adolescent patients in the study. No conclusion on race effect can be made because of the limited number of patients other than Caucasian race available in the study.

Additional Information

Safety update from spontaneous post-marketing reporting identified one pediatric case each of anemia, cutaneous photosensitivity, and elevated leukocyte count. See Medical Officer's reviews (8/20/04 and 10/26/04) for specific labeling recommendations.

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