Clinical Review
NDA 20-333/SE5-008

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Sponsor:	Shire Pharmaceutical Development Inc.
Drug name:	Agrylin (Anagrelide Hydrocholoride)
Drug class:	Anti-platelet agent
Indication:	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.
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Medical Reviewer:	Min Lu, M.D., M.P.H.

Table of Contents

Table of Contents **2**

Executive Summary **6**

I. Recommendations **6**

A. Recommendation on Approvability 6

B. Recommendation on Phase 4 Studies and/or Risk Management Steps 6

II. Summary of Clinical Findings **6**

A. Brief Overview of Clinical Program 6

B. Efficacy 6

C. Safety 7

D. Dosing 10

E. Special Populations 10

Clinical Review **12**

I. Introduction and Background **12**

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups 12

B. State of Armamentarium for Indication(s) 12

C. Important Milestones in Product Development 12

D. Other Relevant Information 12

E. Important Issues with Pharmacologically Related Agents 12

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews **13**

III. Human Pharmacokinetics and Pharmacodynamics **13**

A. Pharmacokinetics 13

B. Pharmacodynamics 13

IV. Description of Clinical Data and Sources 13

A. Overall Data 13

B. Tables Listing the Clinical Trials 13

C. Postmarketing Experience 14

D. Literature Review 14

V. Clinical Review Methods 14

A. How the Review was Conducted 14

B. Overview of Materials Consulted in Review 14

C. Overview of Methods Used to Evaluate Data Quality and Integrity 14

D. Were Trials Conducted in Accordance with Accepted Ethical Standards. 14

E. Evaluation of Financial Disclosure 14

VI. Integrated Review of Efficacy 15

VII. Integrated Review of Safety 15

A. Brief Statement of Conclusions 15

B. Description of Patient Exposure 15

C. Methods and Specific Findings of Safety Review 19

D. Adequacy of Safety Testing 40

E. Summary of Critical Safety Findings and Limitations of Data 40

VIII. Dosing, Regimen, and Administration Issues 44

IX. Use in Special Populations 44

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation 44

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy 44

C. Evaluation of Pediatric Program 44

D. Comments on Data Available or Needed in Other Populations 44

X. Conclusions and Recommendations 45

A. Conclusions 45

B. Recommendations 45

XI. Appendix 45

A. Adverse Events Reported in the Study 45

B. Label Recommendations 49

LIST OF ABBREVIATION

ADHD	Attention deficit hyperactivity syndrome
AE	Adverse event
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
bid	Twice daily
AUC	Area under the plasma concentration-time curve during the dosing interval
BPM	Beats per minute
Cavg	Average of observed plasma concentrations
Cmax	Maximum observed plasma concentration
Cmin	Minimum observed plasma concentration
CBC	Complete blood count
CI/F	Oral clearance
CML	Chronic myelogenous leukemia
CRF	Case report form
CTC	Common Toxicity Criteria
ECG	Electrocardiogram
ET	Essential thrombocythemia
HR	Heart rate
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulator Activities
MPD	Myeloproliferative disorder
OMPDs	Other myeloproliferative disorders
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Prothrombin
PV	Polycythemia vera
qd	Once daily
qid	Four times daily
SAE	Serious adverse event
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
T 1/2z	Terminal elimination half-life
tmax	Time of occurrence of Cmax
tid	Three times daily

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.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug established and trade name: Agrylin

Drug class: Platelet-reducing agent

Sponsor's proposed indication: 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.

B. State of Armamentarium for Indication(s)

Agrylin is the only drug that has been approved for the 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.

C. Important Milestones in Product Development

Agrylin was approved on March 14, 1997 for the 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 submitted initial Proposed Pediatric Study Request in June 10, 2002, and revised protocol in November 27, 2002. On March 27, 2003, the Agency issued a Written Request for Pediatric Study to the sponsor. In response the Written Request, the sponsor conducted a pediatric clinical study (SPD422-202) and was granted Pediatric Exclusivity on May 25, 2004.

D. Other Relevant Information

Agrylin is marketed in 11 countries currently.

E. Important Issues with Pharmacologically Related Agents

Agrylin is the only available platelet-reducing agent and the mechanism by which Agrylin reduces blood platelet count is still under investigation.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

No new data were submitted for Chemistry, Animal Pharmacology and Toxicology, Microbiology and Statistics.

See Biopharmaceutics review.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

See Clinical Pharmacology and Biopharmaceutics Review, Dr. Tien-Mien Chen, Ph.D., dated 7/14/2004.

B. Pharmacodynamics

See Clinical Pharmacology and Biopharmaceutics Review, Dr. Tien-Mien Chen, Ph.D., dated 7/14/2004.

IV. Description of Clinical Data and Sources

A. Overall Data

The following material in the NDA submission was reviewed:

- NDA SE5-008 volumes 1-10, submitted March 12, 2004
- Amendment Volumes 1-3, submitted May 11, 2004

B. Tables Listing the Clinical Trials

Studies	Type of trials	Number of patients enrolled	Dose regimens	Location of the study
SPD422-202	Multi-center, safety, PK/PD study	17 pediatric patients 7-14 years of age and 18 adult/adolescent patients 16 to 86 years of age	Agrylin maintenance and titration: per previously prescribed dosing -pediatric group: a range of 1mg to 6 mg total daily dose -adult/adolescent group: a range of 0.5 mg to 7mg total daily dose Agrylin naïve: 0.5 mg oral once daily with upward titration in increment of 0.5 mg/day per week	United States, Czech Republic, France, Germany, Poland, Russia, Spain, and South Korea

Reviewer's table

C. Postmarketing Experience

Agrylin is currently marketed in 11 countries.

D. Literature Review

No literature review was provided by the sponsor. A search of PubMed found two papers that published after 1997 reporting a total of 4 children who received anagrelide treatment for ET (Lackner H, et al., J. Pediatr Hematol Oncol 1998 20:469-73; and Scherer S, et al., Pediatr Hematol Oncol 2003; 20:361-5).

V. Clinical Review Methods

A. How the Review was Conducted

One clinical trial was submitted and was reviewed. The trial and other submitted material were evaluated in the integrated safety summary.

B. Overview of Materials Consulted in Review

The datasets of the one study submitted were examined for the efficacy and safety evaluation.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No inspection was done for this supplement.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trial was conducted in accordance with accepted ethical standards. Written informed consents were required from all legally authorized representatives of pediatric patients in the trial. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

E. Evaluation of Financial Disclosure

The sponsor certified that there was no financial arrangement with clinical investigators, who conducted the clinical trial (Form FDA 3454).

VI. Integrated Review of Efficacy

Efficacy was not studied in the trial. 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).

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

One safety, PK and 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 a similar frequency and types of adverse events in pediatric patients as compared to adult patients.

B. Description of Patient Exposure

Prior exposure

Most (82.9%; 29/35) patients had prior anagrelide exposure before the study. At study entry, 6 (17.1%) patients were anagrelide naive, 6 (17.1%) patients were on anagrelide titration, and 23 (65.7%) patients were on anagrelide maintenance. Only one (5.9%) patient was anagrelide naïve at study entry in the pediatric group as compared to 5 (27.8%) in the adult group.

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.

Exposure on study

The mean duration of exposure on the study was 91.5 days, which was similar for the pediatric (92.5 days) and adult (90.5 days) groups. All patients received anagrelide for ≥85 days on the study.

Doses and Duration of Anagrelide Treatment on Study by Group

Dose (mg)	Pediatric group		Adult group	
	No.	Duration on study (Days)	No.	Duration on study (days)
0.5- <2.0	8	94.5 (8.0)	12	86.8 (11.0)
2.0- <4.0	6	75.8 (35.2)	7	71.3 (36.6)
4.0- <6.0	3	91.0 (1.0)	0	
6.0- <8.0	1	88.0	1	89.0
Total	17	92.5 (6.6)	18	90.5 (3.2)

Note: one patient may be exposed to two dose levels due to dose titration.
Reviewer's table based on sponsor's table 2.1.1A and 2.1.1B in NDA Vol. 1, p43-44 submitted on May 11, 2004

Overall exposure

Mean overall anagrelide exposure (prior to and on study) 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.

Starting dose and dose adjustments

The median starting dose for each of the pediatric (≤11 years old), adolescent (12-15 years old) and adult (≥16 years old) age groups was 1.0 mg. This remained unchanged with the exclusion of patients who were anagrelide naive at study entry and those who commenced anagrelide dosing at 0.5 mg once daily per protocol. The mean (n; range) starting doses were 1.1 mg (7/ 8 patients; 0.75 mg [alternating daily doses of 0.5 mg and 1 mg] -1.5 mg), 1.1mg (9/ 9 patients; 1.0 mg- 1.5 mg), and 1.2mg (13/ 18 patients; 0.5mg- 2.0mg) for the pediatric (≤ 11 years old), adolescent (12-15 years old) and adult (≥16 years old) age groups, respectively, when patients anagrelide naive at study entry were excluded.

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, 2.0 mg and 1.5mg, respectively. The mean (n; range) doses were 2.1 mg (8/ 8 patients; 1.0 mg- 4.5 mg), 2.6mg (9/ 9 patients; 1.0 mg- 6.0 mg), and 1.9 mg (18/18 patients; 0.5 mg-7.0 mg) for the pediatric (≤ 11 years old), adolescent (12-15 years old) and adult (≥16 years old) age groups, respectively.

The frequency of dose adjustments and the average amount of dose increase (or decrease) were not assessed as the number of patients with dose adjustment data at each described time interval is small and no firm conclusions can be derived.

Starting dose (i.e., first ever anagrelide total daily dose) and final dose (i.e., final on study total daily dose) are summarized below by individual subject and subject group.

Table 6: Starting Dose and Final Dose

Subject Group	Subject Number	Total Daily Starting Dose (mg)	Total Daily Final Dose (mg)	Change from Starting Dose (mg)	Final Dosing Regimen
Pediatric/Adolescent	09-001	1.0	6.0	5.0	3mg bid
	14-001†	1.0	2.5	1.5	1mg qd 0.5mg qd 1mg qd
	14-002	1.0	1.0	0	0.5mg bid
	15-001	1.0	4.5	3.5	1.5mg tid
	17-001	1.5	2.0	0.5	1mg bid
	18-001	1.0	4.0	3.0	1mg qid
	20-001	1.0	1.0	0	0.5mg bid
	23-001	1.0	1.0	0	0.5mg bid
	24-001	0.5*	1.5	1.0	1.5mg qd
	24-002	1.0	3.0	2.0	1mg tid
	27-001	1.5	3.0	1.5	1mg tid
	28-001	1.0	2.0	1.0	1mg bid
	29-001	1.0	2.0	1.0	0.5mg qid
	29-002‡	0.75	4.5	3.75	1.5mg tid
	32-001	1.5	1.0	-0.5	0.5mg bid
	32-002	1.0	1.0	0	0.5mg bid
	32-003	1.0	1.0	0	0.5mg bid
Adolescent/Adult	03-001	2.0	2.0	0	1mg bid
	03-002	1.0	3.0	2.0	1.5mg bid
	03-003	1.0	2.0	1.0	0.5mg qid
	03-005	1.5	2.0	0.5	0.5mg qid
	03-006†	1.5	3.5	2.0	2mg qd 1.5mg qd
	03-007	0.5*	0.5	0	0.5mg qd
	07-001	1.0	1.0	0	0.5mg bid
	07-002	0.5	1.5	1.0	0.5mg tid
	07-003	1.5	1.0	-0.5	1mg qd

Table 6 continued.

Table 6: Starting Dose and Final Dose

Subject Group	Subject Number	Total Daily Starting Dose (mg)	Total Daily Final Dose (mg)	Change from Starting Dose (mg)	Final Dosing Regimen
	07-004	0.5*	1.0	0.5	0.5mg bid
	07-005	0.5*	1.5	1.0	0.5mg tid
	07-006	0.5*	0.5	0	0.5mg qd
	10-001	1.0	3.0	2.0	1mg tid
	10-002	1.0	2.0	1.0	1mg bid
	10-003	1.5	0.5	-1.0	0.5mg qd
	10-004	0.5*	0.5	0	0.5mg qd
	11-001#,†	1.0	7.0	6.0	4mg qd 3mg qd
	21-002	0.5	1.0	0.5	0.5mg bid
Pediatric	Median	1.0	1.25	0.5	na
	Mean	1.0	2.1	1.1	
	SD	0.3	1.5	1.6	
Adolescent	Median	1.0	2.0	1.0	na
	Mean	1.0	2.6	1.5	
	SD	0.2	1.7	1.8	
Adolescent/Adult	Median	1.0	1.5	0.5	na
	Mean	1.0	1.9	0.9	
	SD	0.4	1.6	1.5	

* Subjects naïve at study entry commenced anagrelide therapy at 0.5mg qd per protocol.
# This subject received single doses in excess of the recommended 2.5mg.
† Subjects received bid or tid regimen of unequal individual doses.
‡ Subject received alternating daily doses of 0.5mg and 1mg.
na=not applicable
Pediatric (≤11 years old); adolescent (12-15 years old); adolescent/adult (≥16 years old)
Source: Appendix 2, Listing 1.1, Listing 7.3, and Listing 7.4

Sponsor's table in NDA Vol. 1, p 8-9 submitted on May 11, 2004

Reviewer's comments: In current label, the recommended starting dosage is 0.5 mg qid or 1.0 mg bid based on clinical trials in adult patients. In this study, it seems that all pediatric patients (16) and the majority of adult patients(12/13) started at a lower dose than the recommended total daily dose based on retrospective review in patients with prior anagrelide exposure. The majority of pediatric patients(75%, 12/16) started at one-half of recommended dose (1 mg), and nearly 50% of adult patients (6/13) also started 1 mg total daily dose. For final total daily dose, about 60% of pediatric (10/16) and adult (8/13) patients used 2 mg or more total daily dose based on retrospective review in patients with prior anagrelide exposure. This suggests that some patients may not need to start at the recommended dose because they may have platelet

count under control below the recommended starting dose. This also suggests that most clinicians use a lower dose as starting dose and titrated up as needed to achieve clinical response in patients, especially in pediatric patients. However, this conclusion is limited by the small number of patients available in the study and the retrospective review of data.

C. Methods and Specific Findings of Safety Review

Study SPD422-202

Study Protocol

Study Objectives

Primary objective:

- To assess the safety and tolerability of anagrelide in pediatric/adolescent (≤ 15 years old) subjects with thrombocythemia secondary to MPDs and compare with the safety and tolerability of anagrelide in adolescent/adult (≥16 years old) subjects with thrombocythemia secondary to MPDs.

Secondary objectives:

- To assess the steady state PK profile of anagrelide in pediatric/adolescent (≤ 15 years old) subjects with thrombocythemia secondary to MPDs, and compare with the steady state PK profile of anagrelide in adolescent/adult (≥ 16 years old) subjects with thrombocythemia secondary to MPDs.
- To determine the correlation, if any, between anagrelide daily dose, resultant anagrelide plasma concentrations, and platelet count in pediatric/ adolescent (≤ 15 years old) subjects and adolescent/adult (≥ 16 years old) subjects with thrombocythemia secondary to MPDs.
- To assess data on the starting dose of anagrelide, dose adjustments, and platelet counts of pediatric/adolescent (≤ 15 years old) subjects and adolescent/ adult (≥ 16 years old) subjects with thrombocythemia secondary to MPDs.

Study Design

This was a multicenter, safety, pharmacokinetic (PK), and pharmacodynamic (PD) study.

Study Population

Inclusion criteria:

1. Pediatric subjects, aged ≤ 11 years old; adolescent subjects, aged 12 to 15 years old inclusive; and adolescent/adult subjects, aged ≥16 years old.
2. Male, or female subjects who were post- menopausal (a menorrhagic for at least 12 months), or surgically or biologically sterile. Females of childbearing potential with a negative urine

pregnancy test prior to entering the study and using adequate forms of contraception for the duration of the study (i.e., from Screening through the last study visit) or abstaining from sexual activity. Males were to avoid fathering children during the course of the study, and adequate methods of contraception were to be used by both male and female subjects. Adequate methods of contraception were double barrier methods (condoms with spermicidal jelly or foam, and diaphragm with spermicidal jelly or foam), oral, depot and injectable contraceptives, intrauterine device, and surgical sterilization. If hormonal contraceptives were utilized (oral, implanted, or injectable), the period of use was to be sufficiently long to achieve pharmacological effectiveness prior to study drug exposure (refer to individual product information for details of onset of effectiveness). Single barrier methods, rhythm methods, or sterility of a partner were not considered adequate contraception. If subject was not currently sexually active, the subject must have agreed to use acceptable contraception (as defined above) if the subject decided to become sexually active during the period of study drug exposure.

3. Body weight must have been between 5th and 95th percentile on National Center for Health Statistics (NCHS) growth chart for age, height, and weight for pediatric/adolescent subjects. Adult body weight must have been between 10% below and 20% above ideal weight for the subject's height and estimated frame size according to the Metropolitan Life Insurance Company Statistical Bureau Tables.
4. Diagnosis of ET, PV, CML, or OMPDs.
5. History of thrombocythemia secondary to MPDs treated with or without anagrelide therapy.
6. Free of active infection.
7. Adequate renal function (serum creatinine ≥ 2mg/ dL).
8. Adequate hepatic function (aspartate aminotransferase [AST] and bilirubin ≤1.5 x upper limit of normal).
9. Performance status of 0 or 1 (World Health Organization [WHO] criteria), with a life expectancy of ≥ 4 months.
10. Voluntary documented consent and assent (for pediatric/ adolescent subjects in accordance with local and national requirements) to participate in this study.

Exclusion criteria:

1. Any significant disease or condition that was judged by the Investigator to pose unacceptable risk to the subject or prevented the subject from completing the study or impacted the validity of the study results.
2. A resting ejection fraction below the lower limit of the laboratory normal.
3. Any history of drug or alcohol abuse.
4. Current use of tobacco in any form (e.g., smoking, chewing).
5. History of allergic or adverse response to any related drug.
6. Participation in a previous clinical trial within 30 days prior to study initiation.
7. Blood donation of one pint or more within 30 days prior to study initiation.
8. Plasma donation within seven (7) days prior to study initiation.
9. Abnormal diet or substantial changes in eating habits within 30 days (per Investigator discretion) prior to study initiation.

10. Treatment with any known enzyme altering agents (barbiturates, phenothiazines, cimetidine, etc.) within 30 days prior to or during the study.
11. Positive urine pregnancy test (for females of child-bearing potential) at Screening.
12. Females who were breastfeeding.
13. A positive urine screen for alcohol or drugs of abuse.

Study Treatment

All study medication was supplied by the Sponsor and distributed (b) (4) to the pharmacist/designee at each participating center.

Study drug was supplied as opaque, white capsules containing 0.5mg or 1 mg of anagrelide hydrochloride for oral administration.

For subjects receiving a stable maintenance dose of anagrelide at study entry or undergoing anagrelide dose titration, study drug was dosed per previously prescribed anagrelide daily dose and regimen. Subjects who were anagrelide naive started study drug dosing at 0.5mg qd. For subjects who were anagrelide naive or undergoing anagrelide dose titration at study entry, upward titration in increments of 0.5mg/day in a week was allowed. Downward titration was per investigator discretion. During the Day 30 PK study period, the study drug reference dose was administered in the confines of the clinic under the direction of designated personnel.

Antineoplastic or cytotoxic agents and ionizing radiation were allowed if needed to treat proliferative processes other than thrombocythemia. However, if the agent was known to affect platelet counts, then it was not to be added to the subject's treatment regimen while the subject was participating in the study. Drugs known to affect platelet count included, but were not limited to chlorambucil, busulfan, hydroxurea, radioactive phosphorous (^{32}p), and interferon-α.

Subjects were instructed to bring their study drug and bottle to every visit. Compliance was assessed by capsule counts at the Day 30 and Study Completion (Day 90)/ Early Termination visits. Details were recorded by the pharmacist/nominated person on the drug accountability logs and in the CRF.

Safety Assessments

The following safety assessments were included in the study.

- **Physical examination**

A complete physical examination was performed at Screening and at Study Completion (Day 90)/ Early Termination of the study. Height was measured at Screening and weight was measured at Screening, Day 1, Day 30, and Study Completion (Day 90)/ Early Termination.

- **Vital signs**

Sitting vital signs (blood pressure, heart rate, respiratory rate, and temperature) were performed at Screening and at Study Completion (Day 90)/ Early Termination of the study. In addition,

heart rate and blood pressure were measured 15 minutes prior to the 12-lead ECG performed on Day 1 and Day 15 (only for anagrelide naive or titrating subjects), and on Day 30 approximately 15 minutes prior to the 0-hour dose and approximately 15 minutes prior to each scheduled PK blood draw.

- **EGG**

A 12-lead ECG was performed at Screening, Day 1, and Study Completion (Day 90)/Early Termination at the same time of the day for each visit for all subjects. For subjects who were anagrelide naive or undergoing dose titration at study entry, a 12-lead ECG was performed on Day 15 and ambulatory ECG monitoring was also performed on Day -1. Twenty-four-hour ambulatory ECG monitoring was performed on all subjects commencing prior to the 0-hour dose on Day 30. Ambulatory ECG data was reviewed and interpreted by a central laboratory.

- **Echocardiogram**

Cardiac function was assessed by use of echocardiogram at Screening, Day 30, and Study Completion (Day 90)/ Early Termination. Any clinically relevant finding following interpretation of the echocardiogram was to be documented in the medical record and CRF page. If a new clinically significant finding occurred (not noted at Screening) after the Screening examination, an AE form was completed. If there was a decline in the resting ejection fraction below the lower limit of the laboratory normal or ≥ 20% of the baseline value but the subject remained asymptomatic, it was not necessary to discontinue the study drug. Resolution of any abnormal findings during the study was noted in the medical record and CRF.

- **Clinical laboratory evaluation**

Hematology with complete blood count (CBC) (including prothrombin time [PT] and activated partial thromboplastin time [aPTT]), serum chemistry, and urinalysis (with microscopic examination if protein and/or blood detected) was obtained at Screening, Day 30 and Study Completion (Day 90)/ Early Termination. In addition, platelet count, PT and aPTT were obtained on Day 1 for all subjects and on Day 15 for subjects who were anagrelide naive or undergoing anagrelide dose titration at study entry. A urine pregnancy test, for all females who were of childbearing potential, was performed at Screening, Day -1 (for anagrelide naive subjects and subjects undergoing anagrelide dose titration at study entry) or Day 1 (for subjects on anagrelide maintenance therapy), and at Study Completion (Day 90)/ Early Termination.

Reference ranges were supplied by the local laboratory and used to assess the laboratory data for clinical significance and out of range pathological changes. Changes from Screening were recorded as AEs if clinically significant.

- **Adverse events**

Serious and non-serious AEs were recorded at each time point at each visit during the study. Worsening of pretreatment events, after initiation of investigational product, were recorded as new AEs. All AEs reported by the subject were recorded in the source document and on the CRF. Adverse events were reported whether or not they were considered by the Investigator to be related to the study drug. In addition, for anagrelide-experienced subjects, historic data on AEs were collected.

The medical assessment of intensity was determined by using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 2.0 Toxicity Scale regardless of causality at each assessment. When recording AEs on the CRF page, the intensity to be recorded was the worst intensity experienced during the course of the event.

Statistical Methods

In this study, the primary analytical approach for analyses of both safety endpoints and PK endpoints was the comparison between the pediatric/ adolescent (≤ 15 years old) group and the adolescent/ adult (≥16 years old) group. In addition to the safety and PK components of this study, analyses of starting dose and dose adjustment, as well as the pharmacodynamic assessments were performed.

Safety analyses

In general, descriptive statistics were performed on the safety measurements. No inferential statistics were attempted to compare the primary safety measurements between the two subject groups (pediatric/adolescent vs. adolescent/adult).

Continuous variables were summarized using the number of observations, mean, standard deviation, minimum, median, and maximum values. Categorical values were summarized using the number of observations and percentages.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 5.1 and were presented for all reported terms recorded in the CRF in relation to either seriousness or relationship to study drug.

Analysis of starting dose and dose adjustment

Subject data (retrospective data in the case of subjects treated with anagrelide prior to study entry) on starting dose and subsequently adjusted doses were summarized. The frequency of dose increase (or decrease) and the average amount of dose increase (or decrease) were summarized by subject groups.

Determination of sample size

Due to the small number of pediatric/adolescent patients with thrombocythemia secondary to MPDs, the number of subjects proposed for this trial was not based on statistical considerations. The study planned to enroll 36 subjects (18 adolescent/adult [≥16 years old] subjects, 10 adolescent [12 to 15 years old inclusive] subjects, and 8 pediatric [≤ 11 years old] subjects) without replacement.

Protocol Amendments

There were two amendments made to the original protocol. Both amendments were made prior to enrollment into the study.

Summary of changes made in the first amendment (dated 13 February 2003) are listed below.

- Added reference to fact study was to be conducted in additional territories outside of the USA.
- With one exception, reference to Agrylin replaced with anagrelide or anagrelide hydrochloride due to fact study was to be conducted in additional territories outside of the USA. Reference to Xagrid, trademark to be used in European countries, added.
- Clarified age range of subject groups.
- Expanded on introduction section and added study rationale. Overnight hospitalization requirement removed, Consent/ assent process clarified. Screening period changed from Day -21 to Day -2 to Day -21 to Day -8, with study drug administration to commence on Day -7. Updated standard to text to current protocol template.

Summary of changes made in the second amendment (dated 22 April 2003) are listed below.

- Age ranges changed per FDA definition.
- Subject numbers for each age group increased from 15 to 18 per FDA recommendation.
- Additional countries where study to be conducted added and SAE reporting hotline numbers added for each country added.
- Screening period changed to Day -14 through Day -2, and treatment period extended to three months on study in line with FDA recommendations.
- Changes made to assessments and timing of assessments per FDA recommendations, including addition of echocardiogram and a safety provision related to acceptable echocardiogram changes.
- Clarified PK sampling time points during a dosing interval.
- Changed entry criteria to include subjects naive to anagrelide therapy.
- Changed protocol starting dose guideline to allow for assessment of lowest dose of anagrelide (anagrelide naive subjects to start at 0.5mg qd rather than per current treatment guidelines). The sponsor indicated that the starting dose was chosen based on the expectation that this study would provide guidance on the identification of an appropriate starting dose for the pediatric population.

Study Patients

Patient Disposition

A total of 35 patients were enrolled from 17 centers in 9 countries in the study. These included 17 pediatric patients (pediatric/adolescent) and 18 adult patients (adult/adolescent). Among these 35 patients, 34 (97.1%) completed three months (Day 90) on the study (16 pediatric patients and 18 adult patients). One pediatric patient (a 7 year-old male) withdrew consent prior to completion of Day 90 assessments. For this patient some safety information including adverse

events and concomitant medication was collected by telephone interview with the subject's parent.

The following table summarizes the patient disposition.

Table 1: Subject Disposition

	Subject Group		
	Pediatric/Adolescent (N=17)	Adolescent/Adult (N=18)	Total (N=35)
Study Subjects			
Enrolled	17 (100%)	18 (100%)	35 (100%)
Completed Day 30	17 (100%)	18 (100%)	35 (100%)
Completed Day 90	16 (94.1%)	18 (100%)	34 (97.1%)
Withdrew consent/assent prior to study completion	1 (5.9%)	0	1 (2.9%)

Source: Appendix 1, Table 1.2.1

Sponsor's table in NDA Vol. 1, p 2 submitted on May 11, 2004

Protocol Deviations

Protocol deviations were reported in 7 of the 35 enrolled subjects, including 4 (23.5%) in the pediatric patient group and 3 (16.7%) in the adult patient group. Protocol deviations included noncompliant (3 in the pediatric group and 1 in the adult group) and violation of inclusion/exclusion criteria (2 in each group). The following table summarizes these protocol deviations.

Table 5: Protocol Deviations

	Subject Group		
	Pediatric/Adolescent (N=17)	Adolescent/Adult (N=18)	Total (N=35)
Number of Enrolled Subjects	17 (100%)	18 (100%)	35 (100%)
Subjects with Protocol Deviation(s)	4 (23.5%)	3 (16.7%)	7 (20.0%)
Protocol Deviations			
Noncompliant*	3 (17.6%)	1 (5.6%)	4 (11.4%)
Violation of Inclusion/Exclusion Criteria	2 (11.8%)	2 (11.1%)	4 (11.4%)
Other, as noted on End of Study page	0	0	0

* Subjects were considered noncompliant if their average drug compliance was less than 80%. Note, compliance not assessed for those subjects who did not return study medication.

Source: Section 15, Table 1.5.1

Sponsor's table in NDA Vol. 2, p 113 submitted on March 12, 2004

Demographic and Other Baseline Characteristics

Demographics

Demographic characteristics are summarized by group in the following table. The mean age for the pediatric group was 11.4 years with a range of 7 to 14 years and for the adult group was 63.4 years with a range of 16 to 68 years. In the adult group, only one patient was under 18 years (at 16 years of age) and most patients were more than 50 years of age. There were similar numbers of males and females in both pediatric and adult groups. The majority of study patients were Caucasians (65% in the pediatric group and 89% in the adult group).

Table 2: Summary of Demographic and Baseline Information

	Subject Group		
	Pediatric/Adolescent (N=17)	Adolescent/Adult (N=18)	Total (N=35)
Age (years)			
N	17	18	35
Mean (SD)	11.4 (2.24)	63.4 (21.76)	38.2 (30.58)
Median	12.0	69.5	16.0
Minimum, Maximum	7, 14	16, 86	7, 86
Age Category			
≤11 years			8 (22.9%)
12 – 15 years			9 (25.7%)
≥16 years			18 (51.4%)
Gender			
Male	8 (47.1%)	9 (50.0%)	17 (48.6%)
Female	9 (52.9%)	9 (50.0%)	18 (51.4%)
Race			
Caucasian	11 (64.7%)	16 (88.9%)	27 (77.1%)
Black	3 (17.6%)	1 (5.6%)	4 (11.4%)
Hispanic	0	1 (5.6%)	1 (2.9%)
Asian/Pacific Islander	3 (17.6%)	0	3 (8.6%)
American Indian	0	0	0
Other	0	0	0
Height (inches)			
N	17	18	35
Mean (SD)	58.79 (6.160)	65.76 (3.930)	62.38 (6.168)
Median	59.45	65.50	63.00
Minimum, Maximum	46.1, 68.1	58.5, 72.0	46.1, 72.0
Weight (lbs)			
N	17	18	35
Mean (SD)	102.9 (32.85)	155.8 (30.05)	130.1 (41.00)
Median	105.8	152.0	132.0
Minimum, Maximum	46, 168	109, 212	46, 212
Primary Diagnosis			
ET	17 (100%)	12 (66.7%)	29 (82.9%)

Table 2 continued.

Table 2: Summary of Demographic and Baseline Information

	Subject Group		
	Pediatric/Adolescent (N=17)	Adolescent/Adult (N=18)	Total (N=35)
PV	0	5 (27.8%)	5 (14.3%)
CML	0	0	0
Other MPD	0	1 (5.6%)	1 (2.9%)
Years Since Primary Diagnosis*			
N	16	14	30
Mean (SD)	3.56 (2.410)	4.92 (5.802)	4.19 (4.310)
Median	4.00	2.70	3.60
Minimum, Maximum	0.2, 7.4	0.1, 19.0	0.1, 19.0
Prior Anagrelide Exposure			
Yes	16 (94.1%)	13 (72.2%)	29 (82.9%)
No	1 (5.9%)	5 (27.8%)	6 (17.1%)
Anagrelide Status at Study Entry			
Anagrelide Naïve	1 (5.9%)	5 (27.8%)	6 (17.1%)
On Anagrelide Titration	3 (17.6%)	3 (16.7%)	6 (17.1%)
On Anagrelide Maintenance	13 (76.5%)	10 (55.6%)	23 (65.7%)

*A minimum of month and year were required for determination of years since diagnosis.
Source: Appendix 1, Tables 1.3.1 and 1.3.2

Sponsor's table in NDA Vol. 1, p 3-4 submitted on May 11, 2004

Disease characteristics

The primary diagnosis for all pediatric patients was ET. For adult patients, most patients was diagnosed with ET (82.9%; 29/ 35) followed by PV (14.3%; 5/ 35). The mean duration from the disease diagnosis to study entry was 3.6 years in the pediatric group and 4.9 years in the adult group.

Six adult patients and five pediatric patients had histories of thrombo-hemorrhagic events and other signs/symptoms of the disease including headache, pruritis, abdominal pain and joint pain.

Prior and concomitant therapy

More adult patients (88.9%) received prior/concomitant medication than did pediatric patients (52.9%). Chronic therapy taken during the study by the adult patients was largely related to the underlying age-related diseases (e.g., cardiac disease, hypertension).

Antithrombotic agents were the most common drug class taken as prior and/or concomitant medication by all enrolled patients (40%). More adult patients (66.7%) took antithrombotic

agents than did pediatric patients (16.7%). Aspirin (81 mg-325 mg/day) was the most common concomitant medication as a platelet aggregation inhibitor (28.6%, 10/35) in patients overall. Significantly more adult patients (50.0%, 9/18) took aspirin than did pediatric patients (5.9%, 1/17). The second most common concomitant medication taken was vitamins (22.9%); again with more adult patients (38.9%) than pediatric patients (5.9%) taking this group of medications.

Seven adult patients received prior therapy with hydroxyurea and/or interferon for the treatment of thrombocythemia secondary to a MPD. Two patients received anagrelide therapy in combination with hydroxyurea. One subject (a 69-year old female with PV), received concomitant therapy of hydroxyurea (500 mg bid) and anagrelide (0.5 mg bid) for three months prior to study entry. Therapy with hydroxyurea was discontinued on Day 1, at which point the Investigator increased anagrelide therapy to 0.5mg tid. A second subject (a 55-year old male also diagnosed with PV, received concomitant therapy of hydroxyurea (500mg bid) and anagrelide (1 mg bid) for approximately 16 months prior to study entry and continued to do so while on study.

Two pediatric patients (a 7-year old male and an 11-year old male) received concomitant chronic therapy for ADHD.

Treatment Compliance

Patients were considered compliant if the compliance rate was > 80%. The following table summarizes those patients with a compliance rate of < 80% on the study. These included 3 pediatric patients and 1 adult patient. The final daily dose was 1 mg, 3 mg, and 3 mg, respectively, for the pediatric patients, and 2 mg for the adult patient. With the exception of two pediatric patients (1 mg and 3 mg daily dose), platelet count was adequately controlled (≤600 x 10^9/L) at the last visit assessment.

Table 5: Subjects with Compliance Rate <80%

Subject Number	Subject Group	Compliance Rate (%)	Platelet Count (10^9/L)
03-005	Adolescent/Adult	58.4	506
14-002	Pediatric/Adolescent	70.8	752
24-002	Pediatric/Adolescent	62.5	468
27-001	Pediatric/Adolescent	75.7	805

Note: Compliance only assessed on subjects who returned unused study medication. Not assessed on subjects 03-001, 03-003, 15-001 and 17-001.

Source: Appendix 2, Listing 7.2 and Listing 13.2

Sponsor's table in NDA Vol. 1, p 7 submitted on May 11, 2004

Safety Results

Adverse Events in the Study

A total of 21 patients (60.0%) reported 54 AEs during the study. 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).

Nine (25.7%) patients reported AEs deemed possibly or probably related to study drug by Investigators during the treatment period. The incidence of related AEs for patients in the pediatric group (17.6%, 3/17) was lower than for patients in the adult group (33.3%, 6/18).

The overall AEs are summarized below.

Table 7: On Study Adverse Events

	Subject Group					
	Pediatric/Adolescent (N=17)		Adolescent/Adult (N=18)		Total (N=35)	
	# (%) Subjects	# of AEs	# (%) Subjects	# of AEs	# (%) Subjects	# of AEs
Total Adverse Events	9 (52.9%)	24	12 (66.7%)	30	21 (60.0%)	54
Possibly/Probably Related to Study Drug	3 (17.6%)	8	6 (33.3%)	14	9 (25.7%)	22
Severe Adverse Events*	0	0	0	0	0	0
Adverse Events Causing Discontinuation of Study Drug	0	0	0	0	0	0
Serious Adverse Events	1 (5.9%)	1	0	0	1 (2.9%)	1
Adverse Events Leading to Death	0	0	0	0	0	0

* Severe AEs included all AEs with intensity 3 or 4 based on the NCI CTC Version 2.0.

Source: Appendix 1, Table 3.3.1

Sponsor's table in NDA Vol. 1, p 12 submitted on May 11, 2004

Adverse events that were reported by all patients at an incidence rate > 5% (2 or more patients) were palpitation, fatigue, pyrexia, dizziness, headache, epistaxis, and urinary incontinence (See table below.

Table 9: Adverse Events with a Reporting Incidence >5%

Adverse Event (Preferred Term)	Subject Group: Pediatric/Adolescent (N=17) # (%) Subjects	Pediatric/Adolescent (N=17) # of AEs	Adolescent/Adult (N=18) # (%) Subjects	Adolescent/Adult (N=18) # of AEs	Total (N=35) # (%) Subjects	Total (N=35) # of AEs
Palpitations	0	0	3 (16.7%)	5	3 (8.6%)	5
Fatigue	1 (5.9%)	1	2 (11.1%)	2	3 (8.6%)	3
Pyrexia	2 (11.8%)	3	0	0	2 (5.7%)	3
Dizziness	0	0	2 (11.1%)	2	2 (5.7%)	2
Headache	2 (11.8%)	2	1 (5.6%)	1	3 (8.6%)	3
Epistaxis	2 (11.8%)	3	0	0	2 (5.7%)	3
Urinary incontinence	0	0	2 (11.1%)	2	2 (5.7%)	2

Note: Percentages are based on the number of enrolled subjects in each subject group.
Source: Appendix 1, Table 3.3.4

Sponsor's table in NDA Vol. 1, p 14 submitted on May 11, 2004

Reviewer's comments: The study 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%). However, this was limited by the number of patients available in the study and the majority of patients already on anagrelide treatment before the study.

All AEs in the study are listed in Appendix A. Injection site hemorrhage and hematoma were only observed in one adult patient (a 79 year old female with ET).

Related Adverse Events 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 pyrexia, 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. The following table lists the possible related AEs by group in the study.

Table 10: Study Drug Related Adverse Events

Adverse Event (Preferred Term)	Subject Group: Pediatric/Adolescent (N=17) # (%) Subjects	Pediatric/Adolescent (N=17) # of AEs	Adolescent/Adult (N=18) # (%) Subjects	Adolescent/Adult (N=18) # of AEs	Total (N=35) # (%) Subjects	Total (N=35) # of AEs
Anemia NOS	1 (5.9)	1	0	0	1 (2.9%)	1
Angina pectoris	0	0	1 (5.6%)	1	1 (2.9%)	1
Palpitations	0	0	3 (16.7%)	5	3 (8.6%)	5
Diarrhea NOS	0	0	1 (5.6%)	1	1 (2.9%)	1
Fatigue	1 (5.9%)	1	2 (11.1%)	2	3 (8.6%)	3
Edema peripheral	1 (5.9%)	1	0	0	1 (2.9%)	1
Pyrexia	1 (5.9%)	2	0	0	1 (2.9%)	2
Dizziness	0	0	1 (5.6%)	1	1 (2.9%)	1
Headache	2 (11.8%)	2	1 (5.6%)	1	3 (8.6%)	3
Anxiety	0	0	1 (5.6%)	1	1 (2.9%)	1
Dyspnea	0	0	1 (5.6%)	1	1 (2.9%)	1
Epistaxis	1 (5.9%)	1	0	0	1 (2.9%)	1
Pruritus	0	0	1 (5.6%)	1	1 (2.9%)	1

Note: Percentages are based on the number of enrolled subjects in each subject group.
Source: Appendix 1, Table 3.3.8

Sponsor's table in NDA Vol. 1, p 15 submitted on May 11, 2004

Reviewer's comments: Again, the difference in frequency in related AEs between pediatric and adult patients may be due to the limited patients available and the most AEs were reported only by one patient.

Signs and symptoms of disease

Symptoms were reported in five pediatric patients and five adult patients and included headache (4), epistaxis (4), abdominal pain (2) and back/joint pain (2). Episodes of gingival bleeding, stiffness in hands, palpable spleen, cutaneous/subcutaneous bruising/bleeding, and pruritis were reported in one subject each. Only two of the nine patients who received concomitant anagrelide and aspirin therapy reported hemorrhagic/bleeding symptoms. Both patients, however, were anagrelide naive at study entry and the hemorrhagic event reported, epistaxis, was present at screening.

Death

There were no deaths reported in the study.

Other Serious Adverse Events (SAEs)

One subject (2.9%, 1/35) reported a serious AE during the study (inhalation of gases from lighter [mother reports]; preferred term of 'poisoning deliberate'). This event was not considered to be related to anagrelide treatment by investigator.

Discontinuation due to Adverse Events

No subject was withdrawn from the study because of an AE.

Retrospective Adverse Events

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).

An overall summary of retrospective AEs is shown in the following table.

Table 8: Retrospective Adverse Events†

	Subject Group					
	Pediatric/Adolescent (N=16)		Adolescent/Adult (N=13)		Total (N=29)	
	# (%) Subjects	# of AEs	# (%) Subjects	# of AEs	# (%) Subjects	# of AEs
Total Adverse Events	8 (50.0%)	37	7 (53.8%)	24	15 (51.7%)	61
Possibly/Probably Related to Study Drug	5 (31.3%)	15	4 (30.8%)	11	9 (31.0%)	26
Severe Adverse Events*	1 (6.3%)	1	0	0	1 (3.4%)	1
Adverse Events Causing Discontinuation of Anagrelide	0	0	1 (7.7%)	4	1 (3.4%)	4
Serious Adverse Events	1 (6.3%)	1	0	0	1 (3.4%)	1

† Retrospective AEs were collected only from subjects who received anagrelide therapy prior to study entry (ie, were on maintenance therapy or undergoing anagrelide dose titration).

* Severe AEs included all AEs with intensity 3 or 4 based on the NCI CTC Version 2.0.

Source: Appendix 1, Table 3.3.12

Sponsor's table in NDA Vol. 1, p 13 submitted on May 11, 2004

The following table presents retrospective AEs reported as possibly or probably related to study drug by investigator. The type of events reported as related to study drug were similar between the pediatric and adult patients. The AEs reported in pediatric patients included palpitations, headache, nausea, vomiting, abdominal pain, back pain, anorexia, fatigue and muscle cramps and in adult patients included tachycardia, palpitations, headache, dizziness, dyspnea, nausea,

abdominal pain, diarrhea, peripheral edema and vascular skin condition. The number of related events was also similar between the pediatric group (40.5%; 15/37) and the adult group (45.8%; 11/24).

Table 11: Retrospective Anagrelide Related Adverse Events

	Subject Group					
	Pediatric/Adolescent (N=16)		Adolescent/Adult (N=13)		Total (N=29)	
Adverse Event (Preferred Term)	# (%) Subjects	# of AEs	# (%) Subjects	# of AEs	# (%) Subjects	# of AEs
Palpitations	2 (12.5%)	2	1 (7.7%)	1	3 (10.3%)	3
Tachycardia NOS	0	0	1 (7.7%)	1	1 (3.4%)	1
Dyspnea	0	0	1 (7.7%)	1	1 (3.4%)	1
Fatigue	2 (12.5%)	2	0	0	2 (6.9%)	2
Dizziness	0	0	2 (15.4%)	2	2 (6.9%)	2
Headache	2 (12.5%)	2	1 (7.7%)	1	3 (10.3%)	3
Nausea	1 (5.9%)	1	1 (7.7%)	1	2 (6.9%)	2
Diarrhea NOS	0	0	1 (7.7%)	1	1 (3.4%)	1
Vomiting	1 (6.2%)	1	0	0	1 (3.4%)	1
Abdominal pain NOS	3 (18.8%)	4	1 (7.7%)	1	4 (13.8%)	5
Anorexia	1 (6.2%)	1	0	0	1 (3.4%)	1
Back pain	1 (6.2%)	1	0	0	1 (3.4%)	1

Sponsor's Table 11 continued.

Table 11: Retrospective Anagrelide Related Adverse Events

	Subject Group					
	Pediatric/Adolescent (N=16)		Adolescent/Adult (N=13)		Total (N=29)	
Adverse Event (Preferred Term)	# (%) Subjects	# of AEs	# (%) Subjects	# of AEs	# (%) Subjects	# of AEs
Muscle cramps	1 (6.2%)	1	0	0	1 (3.4%)	1
Edema peripheral	0	0	1 (7.7%)	1	1 (3.4%)	1
Vascular skin condition	0	0	1 (7.7%)	1	1 (3.4%)	1

Note: Percentages are based on the number of enrolled subjects in each subject group.
Source: Appendix 2, Listing 9.1

Sponsor's table in NDA Vol. 1, p 16-17 submitted on May 11, 2004

One pediatric patient (6.3%), a 12-year old female receiving a total daily anagrelide dose of 4.5 mg, reported a SAE, left maxillary alveolus abscess (preferred term 'tooth abscess') prior to the study. This event was not considered to be related to anagrelide treatment by investigator and did not lead to discontinuation of therapy. The event was resolved following pharmacological and surgical intervention.

One adult patient (7.7%), a 79-year old female receiving a total daily anagrelide dose of 2 mg, experienced four AEs that led to discontinuation of anagrelide prior to study entry. These events (palpitations, peripheral edema, dizziness and dyspnea) were considered mild-moderate in intensity and to be drug related. These events were resolved upon discontinuation of anagrelide therapy. Anagrelide was reinstituted six months later at a reduced dose (total daily dose of 1.5 mg) with no tolerability reported.

Ambulatory 24-hour ECG monitoring

All subjects in both groups had at least one ambulatory 24 hour ECG (Holter) recording on Day 30 and those who were anagrelide naive or undergoing anagrelide dose titration at study entry had an additional recording on baseline (Day -1).

The following table summarizes the mean heart rate (HR) with ranges in all patients by group. The mean heart rate was higher in the pediatric group as compared to the adult group. The sponsor indicated that this was consistent with what is normally found when comparing children with adults.

Table 28: Ambulatory 24 Hour ECG Monitor - Heart Rate

Subject Group	Mean HR Range (bpm)	Minimum HR (bpm)	Maximum HR (bpm)
Pediatric/Adolescent	75-109	41	117
Adolescent/Adult	54-86	39	161

Source: Section 16.3, Listing 12.4.2

Sponsor's table in NDA Vol. 2, p 147 submitted on March 12, 2004

Reviewer's Comments: The maximum HR should be 177 bpm in the Pediatric/Adolescent group based on Sponsor's section 16.3, Listing 12.4.2. The mean heart rate increased 12.5 bpm from baseline in 4 pediatric patients who were anagrelide naïve or on dose titration at study entry *as compared to 3.4 bpm in 8 adult patients* who were anagrelide naïve or on dose titration at study entry.

The results showed that supraventricular premature beats presented in 32 of the 35 enrolled subjects. There were three pediatric patients who had no superventricular beats recorded on the Holter monitor. Most superventricular beats were recorded as single beat. Runs of up to 20 consecutive beats were also recorded mainly in the adult group. These findings were not considered to be of clinical significance by investigator. Among 4 pediatric patients who were

anagrelide naïve or on dose titration, none had superventricular couplet or run. Two adult patients showed increased superventricular premature beats from baseline. The first patient, a 70-year-old male with underlying coronary heart disease, hypertension and a previous myocardial infarction, was anagrelide naive at study entry and had received anagrelide for 4 weeks. The second patient, an 86-year old female with hypertension, was undergoing anagrelide dose titration at study entry and received anagrelide therapy for 237 weeks prior to study entry. This patient switched from initial therapy with hydroxyurea to anagrelide. The investigator discontinued therapy for a period of 14 months due to apparent bone marrow fibrosis and then reinitiated anagrelide therapy. This patient was on study exposure for about 13 weeks.

Ventricular premature beats were recorded more frequently in the adult group. Most ventricular premature beats were recorded as single beat. One pediatric patient, a 10-year-old male with an overall anagrelide exposure of 217 weeks, had frequent single premature beats with one 3 beat run of ventricular tachycardia. The findings were considered not to be clinical significance by investigator. The sponsor indicated that these premature beats arising from one focus are usually not significant in children and young adults in the absence of heart disease. 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.

One adult patient, a 70-year-old male, demonstrated the R on T phenomenon, which in the presence of heart disease is known to be associated with ventricular tachycardia/fibrillation. This patient had coronary heart disease and was undergoing anagrelide dose titration at study entry (anagrelide exposure prior to study entry was 237 weeks, followed by a break from therapy for a period of 14 months and then therapy was reinitiated; the duration on study drug exposure was approximately 13 weeks). The results showed an increase from five single R on T beats on Day-1 (baseline) to 444 single R on T beats on Day 30. The sponsor indicated that these results were obtained using a computer-assisted autowave form classification and in this context, with no runs of ventricular tachycardia, are considered to be not clinical significance.

A 71-year-old female (with known hypertension and an overall anagrelide exposure of 90 weeks, was found to have a rate dependant bundle branch block recording and was considered not to be clinical significant by investigator.

One pediatric patient, a 7-year-old female, was found to have 5 leads detached when she returned to the clinic. A review of the leads that did record showed sinus rhythm, sinus arrhythmia and sinus tachycardia. These are considered to be normal findings in a child of this age by investigator.

Electrocardiograms

Electrocardiograms (ECG) were performed at Day 1, Day 15 (for anagrelide naive patients or patients undergoing anagrelide dose titration at study entry), and Day 90/early termination in the study. The ECGs were timed to correspond approximately to the Tmax of anagrelide, in order to

detect any cardiovascular effects post-dosing. The following table summarizes the number of patients with a change in ECG from screening.

Table 13: Number of Subjects with Changes in the ECG from Screening

	Subject Group					
	Pediatric/Adolescent		Adolescent/Adult		Total	
Visit	AB, WNL	CS	AB, WNL	CS	AB, WNL	CS
Day 1	1/17	0/17	2/18	0/18	3/35	0/35
Day 15*	0/4	0/4	0/8	0/8	0/12	0/12
Day 90/early termination†	2/16	0/16	4/18	0/18	6/34	0/34

Note: AB=abnormal, not clinically significant (within acceptable normal limits [WNL]); CS=abnormal, clinically significant.

*Only completed for subjects anagrelide naïve or undergoing anagrelide dose titration at study entry.

† One pediatric subject did not complete the Day 90/early termination visit.

Source: Appendix 1, Tables 3.6.1

Sponsor's table in NDA Vol. 1, p 23 submitted on May 11, 2004

A total of six patients (2 pediatric and 4 adult patients) had EGG changes 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 included ST/T changes, T wave inversion, long P-R interval in adult patients, and sinus arrhythmia, and incomplete right bundle branch block in pediatric patients (see Table below). These changes were considered to be nonspecific and not to be clinically significant by investigators.

Table 14: ECG Changes Recorded from Baseline

Subject Number	Age (Years)	Sex	Cardiac Status	Anagrelide Status and Treatment Duration	ECG Change
03-002	30	Male	Normal	Maintenance 294 weeks	T wave inversion
03-007	84	Female	Hypertension TIAs	Naïve 90 days	ST/T changes
07-001	68	Female	Hypertension	Maintenance 109 weeks	ST/T changes
07-003	79	Female	Hypertension TIAs	Maintenance 112 weeks	Long, but normal P-R interval
17-001	7	Male	Normal	Maintenance 92 weeks	Sinus arrhythmia
29-001	14	Male	Normal	Maintenance 135 weeks	Normal sinus rhythm; Incomplete right bundle branch block; Within normal limits

Source: Appendix 2, Listing 12.1, Appendix 3

Sponsor's table in NDA Vol. 1, p 24 submitted on May 11, 2004

Echocardiogram

Echocardiograms were performed at screening, on Day 30 and Day 90 in the study. There were 3 pediatric patients who had abnormal echocardiogram at study entry (atrial septal defect, faint mitral regurgitation, and unspecified changes). The following table summarizes the number of patients with a change in echocardiogram interpretation from screening. No new changes from screening were noted at the Day 30 and at end of the study (Day 90) evaluation for all 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 abnormalities not previously present at baseline. The abnormalities observed for the first two patients were minor valvular insufficiency, which were consistent with mild intermittent cardiac dilatation related to the longstanding hypertension in both patients per investigator. The mild left ventricular regurgitation was noted for the third patient, which is consistent with the echocardiographic appearance of mild left ventricular hypertrophy. In addition, this subject was found to have clinically insignificant lipomatous hypertrophy of the inter atrial septum. In absence of any symptoms, these changes were not considered to be clinically significant by investigator.

Table 15: Number of Subjects with Echocardiogram Shifts from Screening

	Subject Group					
	Pediatric/Adolescent		Adolescent/Adult		Total	
Visit	AB	CS	AB	CS	AB	CS
Day 30	0/17	0/17	1/17	0/17	1/34	0/34
Day 90/early termination*	0/16	0/16	2/18	0/18	2/34	0/34

Note: AB=abnormal, not clinically significant; CS=abnormal, clinically significant.
* One pediatric subject did not complete the Day 90/early termination visit.
Source: Appendix 1, Tables 3.6.2

Sponsor's table in NDA Vol. 1, p 26 submitted on May 11, 2004

Vital signs

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 compared with no such episodes in the adult group. Of these observed events, one pediatric patient, an 11 year old male, 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 and no AEs were reported.

Pharmacodynamic analysis showed significant positive correlations were identified between increases in heart rate and corresponding Cmax of anagrelide ($p=0.016$ based on data available in 10 pediatric patients and 4 adult patients) and BCH24426 ($p=0.003$ based on data available in 8 pediatric patients and 3 adult patients). However, no apparent correlation was found between diastolic blood pressure decreases and corresponding Cmax of anagrelide ($p=0.636$ based on data available in 4 pediatric patients and 11 adult patients) and BCH24426 ($p=0.941$ based on data available in 3 pediatric patients and 9 adult patients) (See Clinical Pharmacology and Biopharmaceutics Review, Dr. Tien-Mien Chen, Ph.D., dated 7/14/2004)

Clinical Laboratory Evaluation

In general, the clinically significant elevations noted in the study were considered to be disease-related and not considered as AEs by investigator. For one patient in the adult group, a 16-year old female with ET, the clinically significant low hemoglobin, low hematocrit and low RBC findings were reported as AEs under system organ class investigations. The events were considered not to be related to study drug. No action was taken with study drug and the event resolved without sequelae. For another patient, a 13-year old male with ET, an increase in cholesterol was observed during the Day 30 assessments (from 5.1 mmol/L to 5.4 mmol/L

[reference normal range 3.5-5.1 mmol/L] and was reported as an AE under system organ class investigations. The patient was treated with non-pharmacologic measures. The event was unresolved and was considered not to be related to study drug by investigator. One pediatric patient on anagrelide maintenance treatment experienced a substantially elevated PT value on Day 1, prior and subsequent assessments were normal.

Pharmacodynamic analysis showed decreases in platelet count were significantly correlated with anagrelide and its active metabolite (BCH24426) when the evaluable data from patients in both pediatric (12 patients) and adult (9 patients) groups were combined ($p=0.027$). No significant levels in correlations were found in either pediatric or adult group alone. Statistically significant positive correlation was also found ($p<0.01$) for the AUC values of BCH24426 and platelet counts. (See Clinical Pharmacology and Biopharmaceutics Review, Dr. Tien-Mien Chen, Ph.D., dated 7/14/2004)

Physical examinations

There were no differences in the baseline status of pediatric patients compared with adult patients. New physical examination abnormalities were observed in four patients (one pediatric [transient flow murmur] and three adult patients [left thigh hematoma, spleen 1-2 cm at left costal margin, or trigger point soreness of multiple areas on the back]) at the end of study. These findings were not considered clinically significant by investigator.

Literature Review

No literature review was provided by the sponsor. A search of PubMed found two papers that published after 1997 reporting a total of 4 children who received anagrelide treatment for ET (Lackner H, et al., J. Pediatr Hematol Oncol 1998 20:469-73; and Scherer S, et al., Pediatr Hematol Oncol 2003; 20:361-5). The reported adverse events included mild transient abdominal side effect and anemia in two different children.

D. Adequacy of Safety Testing

Safety testing of anagrelide in pediatric patients was limited because the number of pediatric patients available in the study and almost all pediatric patients had received anagrelide at study entry. Considering the low incidence of disease in children (0.7-0.8 per million for myeloproliferative disorders [combined ET, PV, and CML], Hasle, et al., British J. of Hematology 1999; 106:1027-1032), it appears that the sponsor made adequate effort to recruit patients (17 pediatric patients from 9 countries) in the study.

E. Summary of Critical Safety Findings and Limitations of Data

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.

VIII. Dosing, Regimen, and Administration Issues

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.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

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.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

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 were 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.

C. Evaluation of Pediatric Program

This submission includes the pediatric study report submitted in response to Written Request for Pediatric Studies.

D. Comments on Data Available or Needed in Other Populations

There are no comments regarding other populations at this time.

X. Conclusions and Recommendations

A. Conclusions

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. Recommendations

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.

XI. Appendix

A. Adverse Events Reported in the Study

Adverse Events Reported in the Study

(Sponsor's table in NDA Vol. 1, p 75-77 submitted in May 11, 2004)

Table 3.3.4 Summary of Adverse Events by System Organ Class and Preferred Term (All Enrolled Subjects)

System Organ Class/ Preferred Term	Subject Group: Pediatric/Adolescent (N=17) Reported by # (%) Subj	Pediatric/Adolescent (N=17) # AEs Reported	Adolescent/Adult (N=18) Reported by # (%) Subj	Adolescent/Adult (N=18) # AEs Reported	Total (N=35) Reported by # (%) Subj	Total (N=35) # AEs Reported
Total	9 (52.9%)	24	12 (66.7%)	30	21 (60.0%)	54
Blood and lymphatic system disorders	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Anaemia NOS	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Cardiac disorders	0 (0.0%)	0	3 (16.7%)	6	3 (8.6%)	6
Angina pectoris	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Palpitations	0 (0.0%)	0	3 (16.7%)	5	3 (8.6%)	5
Ear and labyrinth disorders	0 (0.0%)	0	2 (11.1%)	2	2 (5.7%)	2
Ear pain	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Tinnitus	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Gastrointestinal disorders	2 (11.8%)	2	1 (5.6%)	1	3 (8.6%)	3
Diarrhoea NOS	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Toothache	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Vomiting NOS	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
General disorders and administration site conditions	3 (17.6%)	5	3 (16.7%)	3	6 (17.1%)	8
Fatigue	1 (5.9%)	1	2 (11.1%)	2	3 (8.6%)	3
Injection site haemorrhage	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Oedema peripheral	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Pyrexia	2 (11.8%)	3	0 (0.0%)	0	2 (5.7%)	3
Infections and infestations	4 (23.5%)	7	2 (11.1%)	2	6 (17.1%)	9
Cellulitis	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Gastroenteritis NOS	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Influenza	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Nasopharyngitis	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Pharyngitis viral NOS	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Sinusitis NOS	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Upper respiratory tract infection NOS	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Viral infection NOS	1 (5.9%)	2	0 (0.0%)	0	1 (2.9%)	2
Injury, poisoning and procedural complications	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Poisoning deliberate	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1

Note: Percentages are based on the number of enrolled subjects in each subject group.

Source: SHIRE_422202:[PRODUCTION.STAT.TABLE]SAEORG.SAS, (b) (4) (US). Run 22APR2004 08:50

Table 3.3.4 Summary of Adverse Events by System Organ Class and Preferred Term (All Enrolled Subjects)

System Organ Class/ Preferred Term	Subject Group: Pediatric/Adolescent (N=17) Reported by # (%) Subj	Pediatric/Adolescent (N=17) # AEs Reported	Adolescent/Adult (N=18) Reported by # (%) Subj	Adolescent/Adult (N=18) # AEs Reported	Total (N=35) Reported by # (%) Subj	Total (N=35) # AEs Reported
Investigations	1 (5.9%)	1	2 (11.1%)	4	3 (8.6%)	5
Blood cholesterol increased	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Haematocrit decreased	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Haemoglobin decreased	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Heart rate increased	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Red blood cell count decreased	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Musculoskeletal and connective tissue disorders	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Fibromyalgia	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Nervous system disorders	2 (11.8%)	2	4 (22.2%)	4	6 (17.1%)	6
Dizziness	0 (0.0%)	0	2 (11.1%)	2	2 (5.7%)	2
Headache	2 (11.8%)	2	1 (5.6%)	1	3 (8.6%)	3
Memory impairment	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Psychiatric disorders	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Anxiety	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Renal and urinary disorders	0 (0.0%)	0	2 (11.1%)	3	2 (5.7%)	3
Micturition urgency	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Urinary incontinence	0 (0.0%)	0	2 (11.1%)	2	2 (5.7%)	2
Respiratory, thoracic and mediastinal disorders	3 (17.6%)	5	1 (5.6%)	1	4 (11.4%)	6
Dyspnoea	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Epistaxis	2 (11.8%)	3	0 (0.0%)	0	2 (5.7%)	3
Rhinitis allergic NOS	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Rhinorrhoea	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Skin and subcutaneous tissue disorders	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Pruritus	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Vascular disorders	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1
Haematoma NOS	0 (0.0%)	0	1 (5.6%)	1	1 (2.9%)	1

Note: Percentages are based on the number of enrolled subjects in each subject group.

Source: SHIRE_422202:[PRODUCTION.STAT.TABLE]SAEORG.SAS, (b) (4) (US). Run 22APR2004 08:50

Table 3.3.5 Summary of Serious Adverse Events by System Organ Class and Preferred Term (All Enrolled Subjects)

System Organ Class/ Preferred Term	Subject Group: Pediatric/Adolescent (N=17) Reported by # (%) Subj	Pediatric/Adolescent (N=17) # AEs Reported	Adolescent/Adult (N=18) Reported by # (%) Subj	Adolescent/Adult (N=18) # AEs Reported	Total (N=35) Reported by # (%) Subj	Total (N=35) # AEs Reported
Total	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Injury, poisoning and procedural complications	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1
Poisoning deliberate	1 (5.9%)	1	0 (0.0%)	0	1 (2.9%)	1

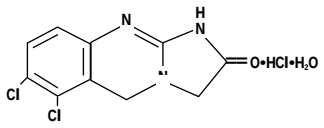
B. Labeling Recommendations

AGRYLIN®
(anagrelide hydrochloride)

Capsules

Rx only

DESCRIPTION
Name: AGRYLIN® (anagrelide hydrochloride)
Dosage Form: 0.5 mg and 1 mg capsules for oral administration
Active Ingredient: AGRYLIN® Capsules contain either 0.5 mg or 1 mg of anagrelide base (as anagrelide hydrochloride).
Inactive Ingredients: Anhydrous Lactose NF, Crospovidone NF, Lactose Monohydrate NF, Magnesium stearate NF, Microcrystalline cellulose NF, Povidone USP.
Pharmacological Classification: Platelet-reducing agent.
Chemical Name: 6,7-dichloro-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-one monohydrochloride monohydrate.
Molecular formula: $C_{10}H_7Cl_2N_3O \cdot HCl \cdot H_2O$
Molecular weight: 310.55
Structural formula:



Appearance: Off-white powder.

Solubility:		
	Water	Very slightly soluble
	Dimethyl Sulfoxide	Sparingly soluble
	Dimethylformamide	Sparingly soluble

CLINICAL PHARMACOLOGY

The mechanism by which anagrelide reduces blood platelet count is still under investigation. Studies in patients support a hypothesis of dose-related reduction in platelet production resulting from a decrease in megakaryocyte hypermaturation. In blood withdrawn from normal volunteers treated with anagrelide, a disruption was found in the postmitotic phase of megakaryocyte development and a reduction in megakaryocyte size and ploidy. At therapeutic doses, anagrelide does not produce significant changes in white cell counts or coagulation parameters, and may have a small, but clinically insignificant effect on red cell parameters. Platelet aggregation is inhibited in people at doses higher than those required to reduce platelet count. Anagrelide inhibits cyclic AMP phosphodiesterase III (PDEIII), as well as ADP- and collagen-induced platelet aggregation.
Following oral administration of ^{14}C-anagrelide in people, more than 70% of radioactivity was recovered in urine. Based on limited data, there appears to be a trend toward dose linearity between doses of 0.5 mg and 2.0 mg. At fasting and at a dose of 0.5 mg of anagrelide, the plasma half-life is 1.3 hours. The available plasma concentration time data at steady state in patients showed that anagrelide does not accumulate in plasma after repeated administration.

The drug is extensively metabolized; < 1% is recovered in the urine as anagrelide. Two major metabolites have been identified and characterized *in vitro* as an inactive metabolite (RL603) and an active metabolite, 3-hydroxy anagrelide (SPD604).
When a 0.5 mg dose of anagrelide was taken after food, its bioavailability (based on AUC values) was modestly reduced by an average of 13.8% and its plasma half-life slightly increased (to 1.8 hours), when compared with drug administered to the same subjects in the fasted state. The peak plasma level was lowered by an average of 45% and delayed by 2 hours.
Pharmacokinetic (PK) data from fasting pediatric (b) (4) (age range 7-14 years) and (b) (4) adult (age range 16-86 years) patients with thrombocythemia secondary to a myeloproliferative disorder (MPD), indicate that **dose- and body weight-normalized** exposure, C_{max} and AUC_{τ}, of anagrelide were lower in the pediatric (b) (4) patients compared to the (b) (4) adult patients (C_{max} 48%, AUC_{τ} 55%). (b) (4) There were no differences in exposure to 3-hydroxy anagrelide. There were no apparent differences between patient groups for t_{max} and $t_{1/2}$ for anagrelide, 3-hydroxy anagrelide, or the inactive metabolite. (b) (4)

CLINICAL STUDIES

A total of 942 patients with myeloproliferative disorders including 551 patients with Essential Thrombocythemia (ET), 117 patients with Polycythemia Vera (PV), 178 patients with Chronic Myelogenous Leukemia (CML), and 96 patients with other myeloproliferative disorders (OMPD), were treated with anagrelide in three clinical trials. Patients with OMPD included 87 patients who had Myeloid Metaplasia with Myelofibrosis (MMM), and 9 patients who had unknown myeloproliferative disorders.

Clinical Studies

Patients with ET, PV, CML, or MMM were diagnosed based on the following criteria:

ET
- Platelet count ≥ 900,000/μL on two determinations
- Profound megakaryocytic hyperplasia in bone marrow
- Absence of Philadelphia chromosome
- Normal red cell mass
- Normal serum iron and ferritin and normal marrow iron stores

CML
- Persistent granulocyte count ≥ 50,000/μL without evidence of infection
- Absolute basophil count ≥ 100/μL
- Evidence for hyperplasia of the granulocytic line in the bone marrow
- Philadelphia chromosome is present
- Leukocyte alkaline phosphatase ≤ lower limit of the laboratory normal range

PV†
- A1 Increased red cell mass
- A2 Normal arterial oxygen saturation
- A3 Splenomegaly
- B1 Platelet count ≥ 400,000/μL, in absence of iron deficiency or bleeding

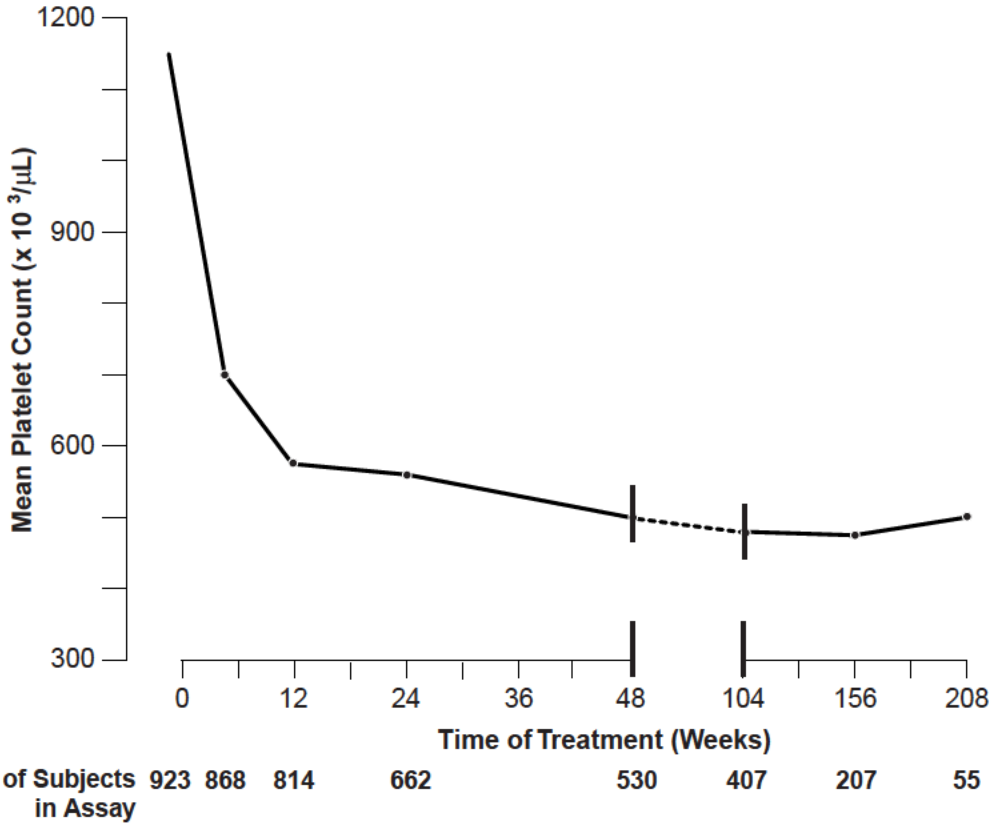
• B2 Leukocytosis (≥ 12,000/μL, in the absence of infection)
• B3 Elevated leukocyte alkaline phosphatase
• B4 Elevated serum B_{12}

† Diagnosis positive if A1, A2, and A3 present; or, if no splenomegaly, diagnosis is positive if A1 and A2 are present with any two of B1, B2, or B3.

MMM
• Myelofibrotic (hypocellular, fibrotic) bone marrow
• Prominent megakaryocytic metaplasia in bone marrow
• Splenomegaly
• Moderate to severe normo-chromic normocytic anemia
• White cell count may be variable; (80,000-100,000/μL)
• Increased platelet count
• Variable red cell mass; teardrop poikilocytes
• Normal to high leukocyte alkaline phosphatase
• Absence of Philadelphia chromosome

Patients were enrolled in clinical trials if their platelet count was ≥ 900,000/μL on two occasions or ≥ 650,000/μL on two occasions with documentation of symptoms associated with thrombocythemia. The mean duration of anagrelide therapy for ET, PV, CML, and OMPD patients was 65, 67, 40, and 44 weeks, respectively; 23% of patients received treatment for 2 years. Patients were treated with anagrelide starting at doses of 0.5-2.0 mg every 6 hours. The dose was increased if the platelet count was still high, but to no more than 12 mg each day. Efficacy was defined as reduction of platelet count to or near physiologic levels (150,000-400,000/μL). The criteria for defining subjects as "responders" were reduction in platelets for at least 4 weeks to ≤600,000/μL, or by at least 50% from baseline value. Subjects treated for less than 4 weeks were not considered evaluable. The results are depicted graphically below:

Patients with Thrombocytosis Secondary to Myeloproliferative Disorders: Mean Platelet Count During Anagrelide Therapy



	Time on Treatment							
		Weeks				Years		
	Baseline	4	12	24	48	2	3	4
Mean*	1131	683	575	526	484	460	437	457
N	923†	868	814	662	530	407	207	55

*x $10^3/\mu L$

† Nine hundred and forty-two subjects with myeloproliferative disorders were enrolled in three research studies. Of these, 923 had platelet counts over the duration of the studies.

AGRYLIN® was effective in phlebotomized patients as well as in patients treated with other concomitant therapies including hydroxyurea, aspirin, interferon, radioactive phosphorus, and alkylating agents.

INDICATIONS AND USAGE

AGRYLIN® Capsules are indicated for the 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 (see CLINICAL STUDIES, DOSAGE and ADMINISTRATION).

WARNINGS

Cardiovascular

Anagrelide should be used with caution in patients with known or suspected heart disease, and only if the potential benefits of therapy outweigh the potential risks. Because of the positive inotropic effects and side-effects of anagrelide, a pre-treatment cardiovascular examination is recommended along with careful monitoring during treatment. In humans, therapeutic doses of anagrelide may cause cardiovascular effects, including vasodilation, tachycardia, palpitations, and congestive heart failure.

Renal

It is recommended that patients with renal insufficiency (creatinine ≥ 2mg/dL) receive anagrelide when, in the physician's judgment, the potential benefits of therapy outweigh the potential risks. These patients should be monitored closely for signs of renal toxicity while receiving anagrelide (see ADVERSE REACTIONS, Urogenital System).

Hepatic

It is recommended that patients with evidence of hepatic dysfunction (bilirubin, SGOT, or measures of liver function >1.5 times the upper limit of normal) receive anagrelide when, in the physician's judgment, the potential benefits of therapy outweigh the potential risks. These patients should be monitored closely for signs of hepatic toxicity while receiving anagrelide (see ADVERSE REACTIONS, Hepatic System).

PRECAUTIONS

Laboratory Tests: Anagrelide therapy requires close clinical supervision of the patient. While the platelet count is being lowered (usually during the first two weeks of treatment), blood counts (hemoglobin, white blood cells), liver function (SGOT, SGPT) and renal function (serum creatinine, BUN) should be monitored.

In 9 subjects receiving a single 5 mg dose of anagrelide, standing blood pressure fell an average of 22/15 mm Hg, usually accompanied by dizziness. Only minimal changes in blood pressure were observed following a dose of 2 mg.

Cessation of AGRYLIN® Treatment: In general, interruption of anagrelide treatment is followed by an increase in platelet count. After sudden stoppage of anagrelide therapy, the increase in platelet count can be observed within four days.

Drug Interactions: Limited PK and/or PD studies investigating possible interactions between anagrelide and other medicinal products have been conducted. *In vivo* interaction studies in humans have demonstrated that digoxin and warfarin do not affect the PK properties of anagrelide, nor does anagrelide affect the PK properties of digoxin or warfarin.

Although additional drug interaction studies have not been conducted, the most common medications used concomitantly with anagrelide in clinical trials were aspirin, acetaminophen, furosemide, iron, ranitidine, hydroxyurea, and allopurinol. There is no clinical evidence to suggest that anagrelide interacts with any of these compounds.

Anagrelide demonstrates some limited inhibitory activity towards CYP1A2 which may present a theoretical potential for interaction with other co-administered medicinal products sharing that clearance mechanism e.g. theophylline.

Anagrelide is an inhibitor of cyclic AMP PDE III. The effects of medicinal products with similar properties such as inotropes milrinone, enoximone, amrinone, olprinone and cilostazol may be exacerbated by anagrelide.
There is a single case report which suggests that sucralfate may interfere with anagrelide absorption.
Food has no clinically significant effect on the bioavailability of anagrelide.
Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate carcinogenic potential of anagrelide hydrochloride. Anagrelide hydrochloride was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y, $TK^{+/-}$) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Anagrelide hydrochloride at oral doses up to 240 mg/kg/day (1,440 mg/m^2/day, 195 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male rats. However, in female rats, at oral doses of 60 mg/kg/day (360 mg/m^2/day, 49 times the recommended maximum human dose based on body surface area) or higher, it disrupted implantation when administered in early pregnancy and retarded or blocked parturition when administered in late pregnancy.
Pregnancy: Pregnancy Category C.
(i) Teratogenic Effects
Teratology studies have been performed in pregnant rats at oral doses up to 900 mg/kg/day (5,400 mg/m^2/day, 730 times the recommended maximum human dose based on body surface area) and in pregnant rabbits at oral doses up to 20 mg/kg/day (240 mg/m^2/day, 32 times the recommended maximum human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to anagrelide hydrochloride.
(ii) Nonteratogenic Effects
A fertility and reproductive performance study performed in female rats revealed that anagrelide hydrochloride at oral doses of 60 mg/kg/day (360 mg/m^2/day, 49 times the recommended maximum human dose based on body surface area) or higher disrupted implantation and exerted adverse effect on embryo/fetal survival.
A perinatal and postnatal study performed in female rats revealed that anagrelide hydrochloride at oral doses of 60 mg/kg/day (360 mg/m^2/day, 49 times the recommended maximum human dose based on body surface area) or higher produced delay or blockage of parturition, deaths of nondelivering pregnant dams and their fully developed fetuses, and increased mortality in the pups born.
Five women became pregnant while on anagrelide treatment at doses of 1 to 4 mg/day. Treatment was stopped as soon as it was realized that they were pregnant. All delivered normal, healthy babies. There are no adequate and well-controlled studies in pregnant women. Anagrelide hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Anagrelide is not recommended in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of child-bearing potential should be instructed that they must not be pregnant and that they should use contraception while taking anagrelide. Anagrelide may cause fetal harm when administered to a pregnant woman.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reaction in nursing infants from anagrelide hydrochloride, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Myeloproliferative disorders are uncommon in pediatric patients and limited data are available in this population. A safety and PK/PD study (See Clinical Pharmacology section) was conducted in 17 pediatric patients 7-14 years of age (8 patients 7-11 years of age and 9 patients 11-14 years of age, mean age of 11 years; 8 males and 9 females) with thrombocythemia secondary to ET as compared to 18 adult patients (mean age of 63 years, 9 males and 9 females). Prior to entry on to the study, 16 of 17 pediatric patients and 13 of 18 adult patients had received anagrelide treatment for an average of 2 years. The starting dose for patients who were already taking anagrelide was determined by retrospective chart review. In these patients, the starting dose of anagrelide ranged from 0.75 mg to 1.5 mg total daily dose in pediatric patients and 0.5 mg to 2 mg total daily dose in adult patients. For patients already on anagrelide, the total daily dose of anagrelide determined at study entry ranged from 1 to 6 mg in pediatric patients (median of 1.25 mg in patients 7-11 years of age and 2 mg in patients 11-14 years of age) and 0.5 to 7 mg for adult patients (median of 1.5 mg). For patients who had been on anagrelide treatment at study entry, the same dose regimens of anagrelide were used in the study for 3 months. For patients who were anagrelide naïve at study entry, the starting dose of anagrelide was 0.5 mg once daily . No overall differences in safety were observed between pediatric patients and adult patients based on the limited number of total patients and anagrelide naïve patients available in the study (See Adverse Reactions section). Efficacy was not evaluated in the study.

In another open-label study , anagrelide had been used successfully in 12 pediatric patients (age range 6.8 to 17.4 years; 6 male and 6 female), including 8 patients with ET, 2 patients with CML, 1 patient with PV, and 1 patient with OMPD. Patients were started on therapy with 0.5 mg qid up to a maximum daily dose of 10 mg. The median duration of treatment was 18.1 months with a range of 3.1 to 92 months. Three patients received treatment for greater than three years.

Geriatric Use: Of the total number of subjects in clinical studies of **AGRYLIN**®, 42.1% were 65 years and over, while 14.9% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Analysis of the adverse events in a population consisting of 942 patients in 3 clinical studies diagnosed with myeloproliferataive diseases of varying etiology (ET: 551; PV: 117; OMPD: 274) has shown that all disease groups have the same adverse event profile. While most reported adverse events during anagrelide therapy have been mild in intensity and have decreased in frequency with continued therapy, serious adverse events were reported in these patients. These include the following: congestive heart failure, myocardial infarction, cardiomyopathy, cardiomegaly, complete heart block, atrial fibrillation, cerebrovascular accident, pericarditis, pericardial effusion, pleural effusion, pulmonary infiltrates, pulmonary fibrosis, pulmonary hypertension, pancreatitis, gastric/duodenal ulceration, and seizure.

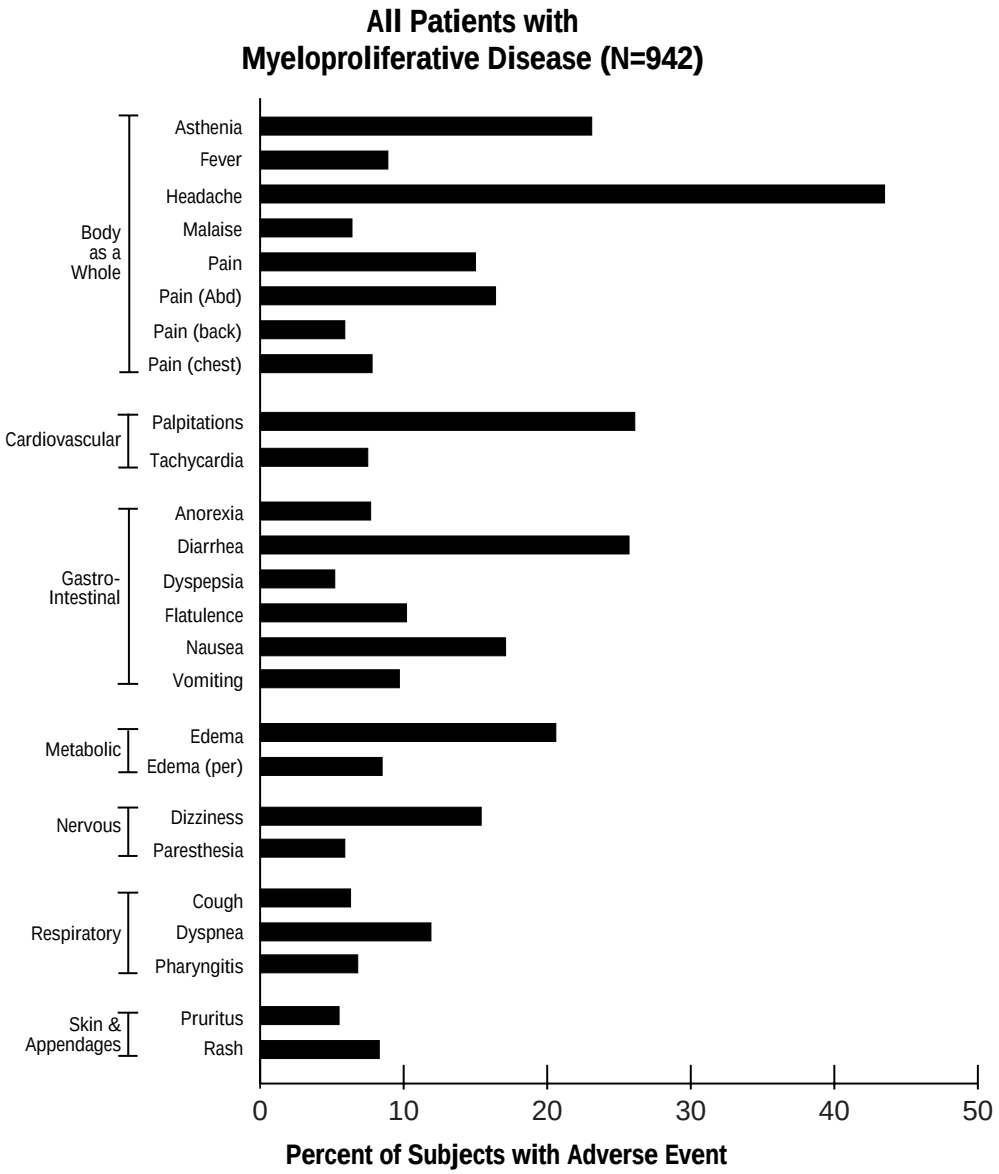
Of the 942 patients treated with anagrelide for a mean duration of approximately 65 weeks, 161 (17%) were discontinued from the study because of adverse events or abnormal laboratory test results. The most common adverse events for treatment discontinuation were headache, diarrhea, edema, palpitation, and abdominal pain. Overall, the occurrence rate of all adverse events was 17.9 per 1,000 treatment days. The occurrence rate of adverse events increased at higher dosages of anagrelide.

The most frequently reported adverse reactions to anagrelide (in 5% or greater of 942 patients with myeloproliferative disease) in clinical trials were:

Headache.....43.5%
Palpitations.....26.1%
Diarrhea.....25.7%
Asthenia 23.1%
Edema, other 20.6%
Nausea.....17.1%
Abdominal Pain 16.4%
Dizziness 15.4%
Pain, other 15.0%
Dyspnea.....11.9%
Flatulence.....10.2%
Vomiting 9.7%
Fever 8.9%
Peripheral Edema.....8.5%
Rash, including urticaria.....8.3%
Chest Pain 7.8%
Anorexia.....7.7%
Tachycardia.....7.5%
Pharyngitis 6.8%
Malaise.....6.4%
Cough.....6.3%
Paresthesia.....5.9%

Back Pain 5.9%
Pruritus.....5.5%
Dyspepsia.....5.2%
Adverse events with an incidence of 1% to < 5% included:
Body as a Whole System: Flu symptoms, chills, photosensitivity.
Cardiovascular System: Arrhythmia, hemorrhage, hypertension, cardiovascular disease, angina pectoris, heart failure, postural hypotension, thrombosis, vasodilatation, migraine, syncope.
Digestive System: Constipation, GI distress, GI hemorrhage, gastritis, melena, aphthous stomatitis, eructation.
Hemic & Lymphatic System: Anemia, thrombocytopenia, ecchymosis, lymphadenopathy. Platelet counts below 100,000/µL occurred in 84 patients (ET: 35; PV: 9; OMPD: 40), reduction below 50,000/µL occurred in 44 patients (ET: 7; PV: 6; OMPD: 31) while on anagrelide therapy. Thrombocytopenia promptly recovered upon discontinuation of anagrelide.
Hepatic System: Elevated liver enzymes were observed in 3 patients (ET: 2; OMPD: 1) during anagrelide therapy.
Musculoskeletal System: Arthralgia, myalgia, leg cramps.
Nervous System: Depression, somnolence, confusion, insomnia, nervousness, amnesia.
Nutritional Disorders: Dehydration.
Respiratory System: Rhinitis, epistaxis, respiratory disease, sinusitis, pneumonia, bronchitis, asthma.
Skin and Appendages System: Skin disease, alopecia.
Special Senses: Amblyopia, abnormal vision, tinnitus, visual field abnormality, diplopia.
Urogenital System: Dysuria, hematuria.

Renal abnormalities occurred in 15 patients (ET: 10; PV: 4; OMPD: 1). Six ET, 4 PV and 1 with OMPD experienced renal failure (approximately 1%) while on anagrelide treatment; in 4 cases, the renal failure was considered to be possibly related to anagrelide treatment. The remaining 11 were found to have pre-existing renal impairment. Doses ranged from 1.5-6.0 mg/day, with exposure periods of 2 to 12 months. No dose adjustment was required because of renal insufficiency.
The adverse event profile for patients in three clinical trials on anagrelide therapy (in 5% or greater of 942 patients with myeloproliferative diseases) is shown in the following bar graph:



Pediatric Patients: In a safety study of 17 pediatric patients 7 to 14 years of age with thrombocythemia secondary to ET as compared to 18 adult patients (See Pediatric Use under Precautions section), the frequency of adverse events observed in pediatric patients was similar to adult patients. The most common adverse events observed in pediatric patients were fever, epistaxis, headache, and fatigue during a 3-months treatment of anagrelide in the study. Adverse events that had been reported in these pediatric patients prior to the study and were considered to be related to anagrelide treatment based on retrospective review were palpitation, headache, nausea, vomiting, abdominal pain, back pain, anorexia, fatigue, and muscle cramps. Episodes of increased pulse rate and decreased systolic or diastolic blood pressure beyond the normal ranges in the absence of clinical symptoms were observed in some patients.

OVERDOSAGE

Acute Toxicity and Symptoms

Single oral doses of anagrelide hydrochloride at 2,500, 1,500 and 200 mg/kg in mice, rats and monkeys, respectively, were not lethal. Symptoms of acute toxicity were: decreased motor activity in mice and rats and softened stools and decreased appetite in monkeys.

There are no reports of overdosage with anagrelide hydrochloride. Platelet reduction from anagrelide therapy is dose-related; therefore, thrombocytopenia, which can potentially cause bleeding, is expected from overdosage. Should overdosage occur, cardiac and central nervous system toxicity can also be expected.

Management and Treatment

In case of overdosage, close clinical supervision of the patient is required; this especially includes monitoring of the platelet count for thrombocytopenia. Dosage should be decreased or stopped, as appropriate, until the platelet count returns to within the normal range.

DOSAGE AND ADMINISTRATION

Treatment with **AGRYLIN**® Capsules should be initiated under close medical supervision. The recommended starting dosage of **AGRYLIN**® for adult patients is 0.5 mg qid or 1 mg bid, which should be maintained for at least one week. There are limited data on the appropriate starting dose for pediatric patients. Starting doses in pediatric patients have ranged from 0.75 mg per day to 0.5 mg qid. In both adult and pediatric patients, dosage should then be adjusted to the lowest effective dosage required to reduce and maintain platelet count below 600,000/µL, and ideally to the normal range. The dosage should be increased by not more than 0.5 mg/day in any one week. Dosage should not exceed 10 mg/day or 2.5 mg in a single dose (see precautions). There are no special requirements for dosing the geriatric population.

To monitor the effect of anagrelide and prevent the occurrence of thrombocytopenia, platelet counts should be performed every two days during the first week of treatment and at least weekly thereafter until the maintenance dosage is reached.

Typically, platelet count begins to respond within 7 to 14 days at the proper dosage. The time to complete response, defined as platelet count ≤ 600,000/µL, ranged from 4 to 12 weeks. Most patients will experience an adequate response at a dose of 1.5 to 3.0 mg/day. Patients with known or suspected heart disease, renal insufficiency, or hepatic dysfunction should be monitored closely.

HOW SUPPLIED

AGRYLIN® is available as:

0.5 mg, opaque, white capsules imprinted "S 063" in black ink:
NDC 54092-063-01 = bottle of 100

1 mg, opaque, gray capsules imprinted "S 064" in black ink:
NDC 54092-064-01 = bottle of 100

Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F), [See USP Controlled Room Temperature]. Store in a light resistant container.

Manufactured for
Shire US Inc.
One Riverfront Place
Newport, KY 41071

By MALLINCKRODT INC.
Hobart, NY 13788

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/s/

Min Lu
8/20/04 11:29:25 AM
MEDICAL OFFICER

Kathy Robie-Suh
8/20/04 12:44:21 PM
MEDICAL OFFICER
Concur. Exact wording of the labeling changes will be negotiated with the sponsor.