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.

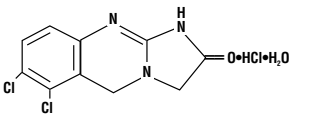
Pharmacological Classification: Platelet-reducing agent.

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 In blood withdrawn from normal volunteers treated with anagrelide, a disruption was found in the postmitotic phase of megakaryocyte development and a reduction in megakaryocyte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. Anagrelide inhibits cyclic AMP phosphodiesterase III (PDEIII). PDEIII inhibitors can also inhibit platelet aggregation. However, significant inhibition of platelet aggregation is observed only at doses of anagrelide higher than those required to reduce platelet count.

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. Two major metabolites have been identified (RL603 and 3-hydroxy anagrelide).

There were no apparent differences between patient groups (pediatric versus adult patients) for t_{max} and $t_{1/2}$ for anagrelide, 3-hydroxy anagrelide, or RL603.

Pharmacokinetic data obtained from healthy volunteers comparing the pharmacokinetics of anagrelide in the fed and fasted states showed that administration of a 1 mg dose of anagrelide with food decreased the C_{max} by 14%, but increased the AUC by 20%.

Pharmacokinetic (PK) data from pediatric (age range 7-14 years) and 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_{t}, of anagrelide were lower in the pediatric patients compared to the adult patients (C_{max} 48%, AUC_{t} 55%).

A pharmacokinetic study at a single dose of 1 mg anagrelide in subjects with severe renal impairment (creatinine clearance <30ml/min) showed no significant effects on the pharmacokinetics of anagrelide.

A pharmacokinetic study at a single dose of 1 mg anagrelide in subjects with moderate hepatic impairment showed an 8-fold increase in total exposure (AUC) to anagrelide.

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.

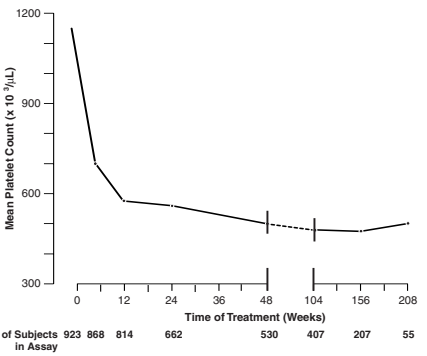
Clinical Studies

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

ET	PV†	MMM
• 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	• 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}	• Myelofibrotic (hypocellular, fibrotic) bone marrow • Prominent megakaryocytic metaplasia in bone marrow • Splenomegaly • Moderate to severe normochromic 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
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	† 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.	

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).

CONTRAINDICATIONS

Anagrelide is contraindicated in patients with severe hepatic impairment. Exposure to anagrelide is increased 8-fold in patients with moderate hepatic impairment (See CLINICAL PHARMACOLOGY). Use of anagrelide in patients with severe hepatic impairment has not been studied. (See also WARNINGS: Hepatic Impairment).

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.

Hepatic

Exposure to anagrelide is increased 8-fold in patients with moderate hepatic impairment (See CLINICAL PHARMACOLOGY). Use of anagrelide in patients with severe hepatic impairment has not been studied. The potential risks and benefits of anagrelide therapy in a patient with mild and moderate impairment of hepatic function should be assessed before treatment is commenced. In patients with moderate hepatic impairment, dose reduction is required and patients should be carefully monitored for cardiovascular effects (See DOSAGE AND ADMINISTRATION for specific dosing recommendations).

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.

An *in vivo* interaction study in humans demonstrated that a single 1mg dose of anagrelide administered concomitantly with a single 900 mg dose of aspirin was generally well tolerated. There was no effect on bleeding time, PT or aPTT. No clinically relevant pharmacokinetic interactions between anagrelide and acetylsalicylic acid were observed. In that same study, aspirin alone produced a marked inhibition in platelet aggregation *ex vivo*. Anagrelide alone had no effect on platelet aggregation, but did slightly enhance the inhibition of platelet aggregation by aspirin.

Anagrelide is metabolized at least in part by CYP1A2. It is known that CYP1A2 is inhibited by several medicinal products, including fluvoxamine, and such medicinal products could theoretically adversely influence the clearance of anagrelide. 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. An open label 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 median starting total daily dose, determined by retrospective chart review, for pediatric and adult ET patients who had received anagrelide prior to study entry was 1mg for each of the three age groups (7-11 and 11-14 year old patients and adults). The starting dose for 6 anagrelide-naive patients at study entry was 0.5mg once daily. At study completion, the median total daily maintenance doses were similar across age groups, median of 1.75mg for patients of 7-11 years of age, 2mg in patients 11-14 years of age, and 1.5mg for adults.

The study evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) profile of anagrelide, including platelet counts (See Clinical Pharmacology 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. Reported AEs were consistent with the known pharmacological profile of anagrelide and the underlying disease. There were no apparent trends or differences in the types of adverse events observed between the pediatric patients compared with those of the adult patients. No overall difference in dosing and safety were observed between pediatric and adult patients.

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. Other adverse events reported in spontaneous reports and literature reviews include anemia, cutaneous photosensitivity and elevated leukocyte count.

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.

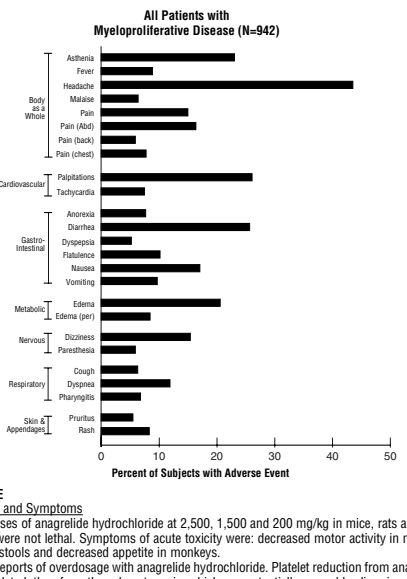
Skin and Appendages System: Skin disease, alopecia.

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:



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. Starting doses in pediatric patients have ranged from 0.5 mg per day to 0.5 mg qid. As there are limited data on the appropriate starting dose for pediatric patients, an initial dose of 0.5 mg per day is recommended. 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. Maintenance dosing is not expected to be different between adult and pediatric patients. 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.

It is recommended that patients with moderate hepatic impairment start anagrelide therapy at a dose of 0.5mg/day and be maintained for a minimum of one week with careful monitoring of cardiovascular effects. The dosage increment must not exceed more than 0.5mg/day in any one-week. The potential risks and benefits of anagrelide therapy in a patient with mild and moderate impairment of hepatic function should be assessed before treatment is commenced. Use of anagrelide in patients with severe hepatic impairment has not been studied. Use of anagrelide in patients with severe hepatic impairment is contraindicated (See CONTRAINDICATIONS).

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.**, 725 Chesterbrook Blvd., Wayne, PA 19087-5637 USA
By MALLINCKRODT INC., Hobart, NY 13788

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