Agrylin® Capsules
(anagrelide hydrochloride)
Rx only

1. DESCRIPTION

Name: AGRYLIN® (anagrelide hydrochloride)

Dosage Form: 0.5 mg capsules for oral administration

Active Ingredient: AGRYLIN® Capsules contain 0.5 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.

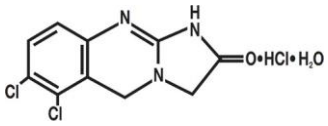
Pharmacological Classification: Platelet-reducing agent.

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
DimethylSulfoxide	Sparingly soluble
Dimethylformamide	Sparingly soluble

2. 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 thrombohemorrhagic events *[see CLINICAL STUDIES (11) and DOSAGE AND ADMINISTRATION (3)]*.

3. DOSAGE AND ADMINISTRATION

3.1 Dosage

Treatment with **AGRYLIN®** Capsules should be initiated under close medical supervision.

Adult and Elderly

The recommended starting dosage of **AGRYLIN®** is 0.5 mg four times daily or 1 mg twice daily (2 capsules of 0.5 mg twice a day).

Pediatrics

There are limited data on the appropriate starting dose for pediatric patients. Starting doses in pediatric patients have ranged from 0.5 mg per day to 0.5 mg four times daily, so an initial dose of 0.5 mg per day is recommended.

Hepatic Impairment

It is recommended that patients with moderate hepatic impairment start anagrelide therapy at a dose of 0.5 mg/day and be maintained for a minimum of one week with careful monitoring of cardiovascular effects. The dosage increment must not exceed more than 0.5 mg/day in any one-week. Anagrelide is contraindicated in severe hepatic impairment. Patients with mild to moderate hepatic impairment should be assessed before and during treatment.

3.2 Titration

Adult: The starting dose should be maintained for at least one week. After one week the dose may be titrated, on an individual basis, to achieve the lowest effective dose required to reduce and/or maintain a platelet count below 600 x 10^9/l and ideally at levels between 150 x 10^9/l and 400 x 10^9/l. The dose increment must not exceed 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.

Pediatrics: The starting dose should be maintained for at least one week. After one week the dose may be titrated, on an individual basis. The dose increment must not exceed 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 WARNINGS and PRECAUTIONS (5)]*

3.3 Monitoring

The effects of treatment with anagrelide must be monitored on a regular basis. If the starting dose is >1 mg/day, platelet counts should be performed every two days during the first week of treatment and at least weekly thereafter until a stable maintenance dosage is reached. Typically, a fall in the platelet count will be observed within 7 to 21 days of starting treatment. The time to complete response, defined as platelet count ≤600,000/µL, ranged from 4 to 12 weeks. In most patients an adequate therapeutic response will be observed and maintained at a dose of 1 to 3 mg/day. In the event of dosage interruption or treatment withdrawal, the rebound in platelet count is variable, but platelet counts typically will start to rise within 4 days and return to baseline levels in one or two weeks, possibly rebounding above baseline values. Therefore platelets should be monitored frequently. Patients with known or suspected heart disease, renal insufficiency, or hepatic dysfunction should be monitored closely.*[see WARNINGS and PRECAUTIONS (5)]*

4. CONTRAINDICATIONS

Contraindicated for use in patients who have known hypersensitivity to anagrelide or any of the other product components.

Anagrelide is contraindicated in patients with severe hepatic impairment.

5. WARNINGS AND PRECAUTIONS

5.1 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 and chronotropic effects and cardiovascular side-effects of anagrelide, 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.

A pre-treatment cardiovascular examination is recommended in all patients. Patients should be monitored during treatment for cardiovascular effects and further investigations carried out as necessary. In humans, therapeutic doses of anagrelide may cause cardiovascular effects, including vasodilation, tachycardia, palpitations, and congestive heart failure.

Anagrelide has been shown to increase the heart rate, resulting in an apparent increase in QTc interval of the electrocardiogram in healthy volunteers. The clinical impact of this effect is unknown *[see CLINICAL PHARMACOLOGY (10)]*.

Caution should be taken when using anagrelide in patients with known risk factors for prolongation of the QT interval, such as congenital long QT syndrome, a known history of acquired QTc prolongation, medicinal products that can prolong QTc interval and hypokalaemia.

Care should also be taken in populations that may have a higher maximum plasma concentration (C_{max}) of anagrelide or its active metabolite, 3-hydroxy-anagrelide, e.g. hepatic impairment or use with CYP1A2 inhibitors *[*see *INTERACTIONS (6)]*.

5.2 Pulmonary Hypertension

Cases of pulmonary hypertension have been reported in patients treated with anagrelide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during anagrelide therapy.

5.3 Bleeding

Use of concomitant anagrelide and acetylsalicylic acid has been associated with major hemorrhagic events.

5.4 Hepatic Impairment

The potential risks and benefits of anagrelide therapy in a patient with mild or moderate impairment of hepatic function should be assessed before and during treatment. In patients with moderate hepatic impairment, dose reduction is required and patients should be carefully monitored for cardiovascular effects *[see DOSAGE AND ADMINISTRATION (3), and CLINICAL PHARMACOLOGY (10)]*.

5.5 Laboratory Monitoring

Therapy requires close clinical supervision of the patient which will include a full blood count (hemoglobin, white blood cell and platelet counts) and assessment of liver function (ALT and AST), renal function (serum creatinine and urea) and electrolytes (potassium, magnesium and calcium).

5.6 Interstitial Lung Diseases

Interstitial lung diseases (including allergic alveolitis, eosinophilic pneumonia and interstitial pneumonitis) have been reported to be associated with the use of anagrelide in post-marketing reports. Most cases presented with progressive dyspnea with lung infiltrations. The time of onset ranged from 1 week to several years after initiating anagrelide. In most cases, the symptoms improved after discontinuation of anagrelide.

5.7 Excipients

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Agrylin as it contains lactose.

5.8 Thrombotic Risk

Abrupt treatment discontinuation or substantial reduction of anagrelide's dose should be avoided due to the risk of sudden increase in platelet counts, which may lead to potentially fatal thrombotic complications, such as cerebral infarction.*[see DOSAGE and ADMINISTRATION (3.2 and 3.3)].*

6. INTERACTIONS

6.1 Effects of Anagrelide on Other Substances

Other PDE3 Inhibitors

Anagrelide is an inhibitor of PDE3. The effects of medicinal products with similar properties such as inotropes milrinone, enoximone, amrinone, olprinone and cilostazol may be exacerbated by anagrelide.

Acetylsalicylic Acid (Aspirin) and Drugs that Increase Bleeding Risk

At therapeutic doses, anagrelide may potentiate the effects of other medicinal products that inhibit platelet aggregation.

Acetylsalicylic acid

In some ET patients concomitantly treated by acetylsalicylic acid and anagrelide, major haemorrhages occurred. Therefore, the potential risks and benefits of concomitant use of anagrelide with aspirin should be assessed, particularly in patients with a high risk profile for

haemorrhage, before treatment is initiated.

In two clinical interaction studies in healthy subjects, co-administration of single-dose anagrelide 1 mg and aspirin 900 mg or repeat-dose anagrelide 1 mg once daily and aspirin 75 mg once daily showed greater *ex-vivo* anti-platelet aggregation effects than administration of acetylsalicyclic acid alone.

Warfarin
In vivo interaction studies in humans have demonstrated that anagrelide does not affect the pharmacokinetic properties of warfarin.

Medicines Metabolized by CYP1A2
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.

Digoxin
In vivo interaction studies in humans have demonstrated that anagrelide does not affect the pharmacokinetic properties of digoxin.

6.2 Effects of Other Substances on Anagrelide
CYP1A2 Inhibitors
Anagrelide and its active metabolite are metabolized 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, thereby increasing plasma concentrations.

CYP1A2 Inducers
CYP1A2 inducers could decrease the exposure of anagrelide. Patients taking concomitant CYP1A2 inducers (e.g. omeprazole) may need to have their dose titrated to compensate for the decrease in anagrelide exposure.

Digoxin or Warfarin
In vivo interaction studies in humans have demonstrated that digoxin and warfarin do not affect the pharmacokinetic properties of anagrelide.

7. ADVERSE REACTIONS
The safety of anagrelide has been examined in 4 open label clinical studies. In 3 of the studies, 942 patients who received anagrelide at a mean dose of approximately 2 mg/day were assessed for safety. In these studies, 22 patients received anagrelide for up to 4 years.

In the later study, 3660 patients who received anagrelide at a mean dose of approximately 2 mg/day were assessed for safety. In this study, 34 patients received anagrelide for up to 5 years. The most commonly reported adverse reactions associated with anagrelide were headache occurring at approximately 14%, palpitations occurring at approximately 9%, fluid retention and nausea both occurring at approximately 6%, and diarrhea occurring at 5%. These adverse drug reactions are expected based on the pharmacology of anagrelide. Gradual dose titration may help diminish these effects.

Adverse reactions arising from clinical studies, post-authorization safety studies and spontaneous reports are presented in the table below. Within the system organ classes they are listed under the following headings: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse Reactions Associated with AGRYLIN® **Italic text denotes post-marketing ADRs*					
MedDRA System Organ Class	Frequency of adverse reactions				
	Very Common	*Common*	*Uncommon*	*Rare*	*Unknown*
Blood and lymphatic system disorders		Anemia	Thrombocytopenia		
Metabolism and nutrition disorders			Anorexia		
Nervous system disorders	Headache	Dizziness Hypoesthesia	Syncope Amnesia Paraesthesia	Migraine Somnolence	
Psychiatric disorders			Depression Confusion Insomnia Nervousness		
Eye disorders				Diplopia Visual abnormal	
Ear and labyrinth disorders				Tinnitus	
Cardiac disorders		Tachycardia Palpitations	Ventricular tachycardia Supraventricular tachycardia Congestive heart failure Atrial fibrillation Arrhythmia	Myocardial infarction Cardiomyopathy Cardiomegaly Pericardial effusion Angina pectoris	**Torsade de pointes*
Respiratory, thoracic and mediastinal disorders			Pleural effusion Dyspnea Epistaxis Pulmonary hypertension	Pulmonary infiltration	**Interstitial lung disease including pneumonitis and allergic alveolitis*
Gastrointestinal disorders		Diarrhea Vomiting Abdominal pain Nausea Flatulence	Gastrointestinal hemorrhage Pancreatitis Dyspepsia Constipation	Gastritis	
Hepatobiliary disorders					**Hepatitis*
Skin and subcutaneous		Rash	Ecchymosis Alopecia		

tissue disorders			Pruritus		
Musculoskeletal and connective tissuedisorders			Arthralgia Myalgia Backpain		
Renal and urinary disorders				Renal failure	*Tubulointertitial nephritis
General disorders and administration site conditions			Edema Chest pain Fever Chills Malaise	Flu-like symptoms Pain Asthenia	
Vascular disorders			Hemorrhage Hypertension	Postural hypotension Vasodilatation	
Infections and infestations			Pneumonia		
Investigations			Hepatic enzymes increased		

8. OVERDOSAGE

8.1 Signs, Symptoms and Laboratory Findings

At higher than recommended doses, anagrelide has been shown to cause reductions in blood pressure, with occasional hypotension.

In post-marketing case reports of intentional overdose with anagrelide, symptoms included sinus tachycardia and vomiting. These symptoms resolved with supportive management.

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.

8.2 Management and Treatment

Close clinical supervision of the patient is required; this especially includes monitoring of the platelet count for thrombocytopenia. If a patient develops thrombocytopenia, dosage should be decreased or stopped until the platelet count returns to within the normal range.

9. SPECIAL POPULATIONS

9.1 Pregnancy

Use of anagrelide is not recommended during pregnancy. Women of child-bearing potential should use adequate birth-control measures during treatment with anagrelide.

Studies in animals have shown reproductive toxicity *[see NON-CLINICAL STUDIES (12)]*. The potential risk for humans is unknown.

There is limited information on the outcome of pregnancies in patients exposed to anagrelide. If anagrelide is used during pregnancy, or if the patient becomes pregnant while

using the medicinal product, she should be advised of the potential risk to the foetus and use of an alternative treatment considered.

9.2 Nursing Mothers

Excretion of anagrelide-related material into milk has been demonstrated in rats.
Because of the potential for adverse reactions in breast-feeding infants, a decision should be made whether to discontinue breast-feeding or to discontinue the drug, taking into account the importance of the drug to the mother.

9.3 Fertility

No human data on the effect of anagrelide on fertility are available. In male rats, there was no effect on fertility or reproductive performance with anagrelide. In female rats, using doses in excess of the therapeutic range, anagrelide disrupted implantation.

9.4 Pediatric Patients

Experience with anagrelide in pediatric patients was based on an open label safety and PK/PD study conducted in 18 pediatric patients aged 7-16 years with thrombocythemia secondary to ET *[see CLINICAL STUDIES (11.2)]*.

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 *[see ADVERSE REACTIONS (7)]*.

9.5 Geriatric Patients

During clinical development approximately 50% of the patients treated with anagrelide were over 60 years of age and no age specific alterations in dose were required in these patients.

Of the 942 subjects in clinical studies of anagrelide, 42.1% were 65 years and over, while 14.9% were 75 years and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

9.6 Hepatic Impairment

Hepatic metabolism represents the major route of anagrelide clearance. Exposure to anagrelide is increased 8-fold in patients with moderate hepatic impairment *[see CLINICAL PHARMACOLOGY (11.3)]* and dose reduction is required *[see DOSAGE AND ADMINISTRATION (3.1)].* Use of anagrelide in patients with severe hepatic impairment has not been studied and is contraindicated. Hepatic function should be assessed before and during treatment.

10. CLINICAL PHARMACOLOGY

10.1 Pharmacodynamics

Pharmacotherapeutic group: Other antineoplastic agents, ATC Code: L01XX35

10.1.1 Mechanism of Action

The precise mechanism by which anagrelide reduces blood platelet count is unknown. In cell culture studies, anagrelide suppressed expression of transcription factors including GATA-1 and FOG-1 required for megakaryocytopoiesis, ultimately leading to reduced platelet production.

10.1.2 Pharmacodynamic Effects

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. The active metabolite, 3-hydroxy anagrelide, has similar potency and efficacy to that of anagrelide in the platelet lowering effect; however, exposure (measured by plasma AUC) to 3-hydroxy anagrelide is approximately 2-fold higher compared to anagrelide.

Anagrelide and 3-hydroxy anagrelide inhibit cyclic AMP phosphodiesterase 3 (PDE3) and 3-hydroxy anagrelide is approximately forty times more potent than anagrelide ($IC50_s$ = 0.9 and 36 nM, respectively). PDE3 inhibition does not alter platelet production. PDE3 inhibitors, as a class can inhibit platelet aggregation. However, significant inhibition of platelet aggregation is observed only at doses of anagrelide higher than those required to reduce platelet count. PDE3 inhibitors have cardiovascular (CV) effects including vasodilation, positive inotropy and chronotropy.

Effects on Heart Rate and QTc Interval

The effect of two dose levels of anagrelide (0.5 mg and 2.5 mg single doses) on the heart rate and QTc interval was evaluated in a double-blind, randomized, placebo- and active-controlled, cross-over study in healthy adult men and women.

A dose-related increase in heart rate was observed during the first 12 hours, with the maximum increase occurring around the time of maximal concentrations. The maximum change in mean heart rate occurred at 2 hours after administration and was +7.8 beats per minute (bpm) for 0.5 mg and +29.1 bpm for 2.5 mg.

An apparent transient increase in mean QTc was observed for both doses during periods of increasing heart rate and the maximum change in mean QTcF (Fridericia correction) was +5.0 msec occurring at 2 hours for 0.5 mg and +10.0 msec occurring at 1 hour for 2.5 mg. The evidence suggests that this increase in QTc may be due to the physiological effect of the increasing heart rate and the corresponding QT-RR hysteresis, rather than a direct effect on repolarization.

10.2 Pharmacokinetics

10.2.1 Absorption

Following oral administration of anagrelide in man, at least 70% of radioactivity was recovered in urine. 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.

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%.

10.2.2 Metabolism

Anagrelide is primarily metabolized by CYP1A2 to form 3-hydroxy anagrelide, which is further metabolized via CYP1A2 to the inactive metabolite,RL603.

10.2.3 Elimination

The plasma half-life of anagrelide is short, approximately 1.5 hours and as expected from its half-life, there is no evidence for anagrelide accumulation in the plasma. Less than 1% of the administered dose is recovered in the urine as anagrelide and approximately 3% and 16-20% of the administered dose is recovered as 3-hydroxy-anagrelide and RL603, respectively.

10.2.4 Linearity

Dose proportionality has been found in the dose range 0.5 mg to 2.5 mg.

10.3 Special Populations Pharmacokinetics

Pediatrics

Pharmacokinetic data from exposed fasting children and adolescents (age range 7 – 16 years) with essential thrombocytopenia (ET) indicate that dose normalized exposure, C_{max} and AUC, of anagrelide tended to be higher in children/adolescents compared with adults. There was also a trend to higher dose-normalized exposure to the active metabolite.

Geriatrics

Pharmacokinetic data from fasting elderly patients with ET (age range 65-75 years) compared to fasting adult patients (age range 22-50 years) indicate that the C_{max} and AUC of anagrelide were 36% and 61% higher respectively in elderly patients, but that the C_{max} and AUC of the active metabolite, 3-hydroxy anagrelide, were 42% and 37% lower respectively in the elderly patients. These differences were likely to be caused by lower presystemic metabolism of anagrelide to 3-hydroxy anagrelide in the elderly patients.

Renal Impairment

A pharmacokinetic study at a single dose of 1 mg anagrelide in subjects with severe renal impairment (creatinine clearance < 30 ml/min) showed no significant effects on the pharmacokinetics of anagrelide. Exposure ($AUC_{0-\infty}$) to the active metabolite of anagrelide, 3-hydroxy-anagrelide, was approximately 50% higher in renally impaired subjects; however, maximum observed plasma concentrations did not differ between the study groups.

Hepatic Impairment

Hepatic metabolism represents the major route of anagrelide clearance. Anagrelide has not been studied in patients with severe hepatic impairment. A pharmacokinetic study at a single

dose of 1 mg anagrelide in subjects with moderate hepatic impairment (Child Pugh score 7-9) showed a 2-fold increase in mean anagrelide C_{max} and an 8-fold increase in mean anagrelide AUC compared to healthy subjects. Additionally, subjects with moderate hepatic impairment showed 24% lower mean 3-hydroxy-anagrelide C_{max} and 77% higher mean 3-hydroxy-anagrelide AUC compared to healthy subjects.

11. 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

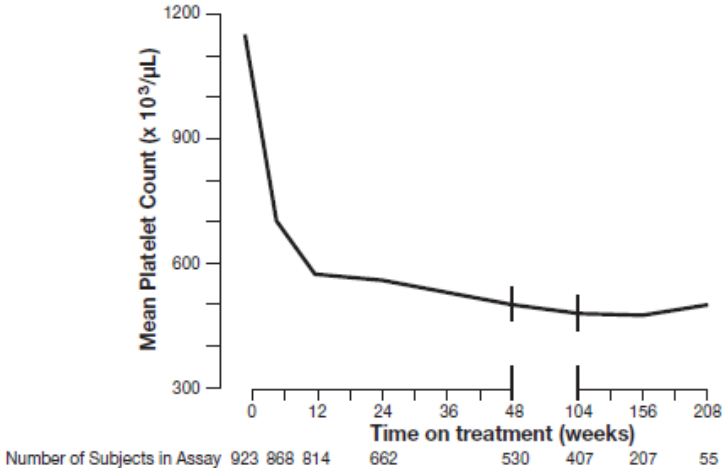
- Myelofibrotic (hypocellular, fibrotic) bone marrow
- Prominent megakaryocytic metaplasia in bone marrow

• Splenomegaly
• Moderate to severe 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

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/µL

† 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.

12. NON-CLINICAL STUDIES

12.1 Carcinogenesis, Mutagenesis

In a two year rat carcinogenicity study a higher incidence of uterine adenocarcinoma, relative to controls, was observed in females receiving 30 mg/kg/day (at least 174 times human AUC exposure after a 1 mg twice daily dose). Adrenal phaeochromocytomas were increased relative to controls in males receiving 3 mg/kg/day and above, and in females receiving 10 mg/kg/day and above (at least 10 and 18 times respectively human AUC exposure after a 1 mg twice daily dose).

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.

12.2 Reproductive Toxicology

Fertility

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.

Embryofetal Development Studies

Maternally toxic doses of anagrelide in rats and rabbits were associated with increased embryo resorption and fetal mortality.

In a pre- and post-natal development study in female rats, anagrelide at oral doses of ≥ 10 mg/kg produced a non-adverse increase in gestational duration. At the NOEL dose (3 mg/kg/day), the AUCs for anagrelide and the metabolites 3-hydroxy-anagrelide and RL603 were 14, 2 and 2-fold higher than the AUC in humans administered an oral dose of anagrelide 2mg/day.

Anagrelide at ≥ 60 mg/kg increased parturition time and mortality in the dam and fetus respectively. At the NOEL dose (30 mg/kg/day), the AUCs for anagrelide and the metabolites 3-hydroxy-anagrelide and RL603 were 425-, 31- and 13-fold higher than the AUC in humans administered an oral dose of anagrelide 2 mg/day, respectively.

In a placental transfer study, a single oral dose of [^{14}C]-anagrelide hydrochloride was administered to pregnant rats on gestation Day 17. Drug-related radioactivity was detected in maternal and fetal tissue.

Lactation
In rats given a single oral dose of [^{14}C] anagrelide hydrochloride, drug related material was detected in the milk, with milk to maternal plasma concentration ratios of up to 3.5 observed.

12.3 Animal Toxicology and/or Pharmacology

In the 2-year rat study, a significant increase in non-neoplastic lesions were observed in anagrelide treated males and females in the adrenal (medullary hyperplasia), heart (myocardial hypertrophy and chamber distension), kidney (hydronephrosis, tubular dilation and urothelial hyperplasia) and bone (femur enostosis). Vascular effects were observed in tissues of the pancreas (arteritis/periarteritis, intimal proliferation and medial hypertrophy), kidney (arteritis/periarteritis, intimal proliferation and medial hypertrophy), sciatic nerve (vascular mineralization), and testes (tubular atrophy and vascular infarct) in anagrelide treated males.

13. PRESENTATION

AGRYLIN® is available as: 0.5 mg, opaque, white capsules imprinted "S 063" in black ink: bottle of 100.

14. STORAGE/SHELFLIFE

Store below 30˚C/4 years at 30˚C.

Indonesian Reg. No. DKI1338900101A1

ON MEDICAL PRESCRIPTION ONLY

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