

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

 **AGRYLIN®**

anagrelide hydrochloride capsules

Capsules, 0.5 mg anagrelide as anagrelide hydrochloride, Oral
Platelet-Reducing Agent

Takeda Canada Inc.
22 Adelaide St. West, Suite 3800
Toronto, Ontario
M5H 4E3

Date of Initial Authorization:
NOV 19, 1997

Date of Revision:
JUL 07, 2021

Submission Control Number: 245876

AGRYLIN® is a registered trademark of Takeda Pharmaceuticals U.S.A., Inc.

TAKEDA™ and the TAKEDA Logo® are trademarks of Takeda Pharmaceutical Company Limited, used under license.

RECENT MAJOR LABEL CHANGES

| | |
|----------------|--|
| Not applicable | |
|----------------|--|

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

| | |
|---|-----------|
| RECENT MAJOR LABEL CHANGES | 2 |
| TABLE OF CONTENTS | 2 |
| PART I: HEALTH PROFESSIONAL INFORMATION | 4 |
| 1 INDICATIONS | 4 |
| 1.1 Pediatrics | 4 |
| 1.2 Geriatrics | 4 |
| 2 CONTRAINDICATIONS | 4 |
| 3 SERIOUS WARNINGS AND PRECAUTIONS BOX | 4 |
| 4 DOSAGE AND ADMINISTRATION | 5 |
| 4.2 Recommended Dose and Dosage Adjustment..... | 5 |
| 4.4 Administration | 6 |
| 4.5 Missed Dose | 6 |
| 5 OVERDOSAGE | 6 |
| 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING | 6 |
| 7 WARNINGS AND PRECAUTIONS | 7 |
| 7.1 Special Populations | 10 |
| 7.1.1 Pregnant Women..... | 10 |
| 7.1.2 Breast-feeding..... | 10 |
| 7.1.3 Pediatrics | 10 |
| 7.1.4 Geriatrics | 10 |
| 8 ADVERSE REACTIONS | 11 |
| 8.1 Adverse Reaction Overview..... | 11 |
| 8.2 Clinical Trial Adverse Reactions | 11 |
| 8.3 Less Common Clinical Trial Adverse Reactions | 12 |

| | | |
|--|---|-----------|
| 8.4 | Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings | 13 |
| 8.5 | Post-Market Adverse Reactions..... | 14 |
| 9 | DRUG INTERACTIONS..... | 14 |
| 9.2 | Drug Interactions Overview | 14 |
| 9.4 | Drug-Drug Interactions..... | 14 |
| 9.5 | Drug-Food Interactions | 15 |
| 9.6 | Drug-Herb Interactions..... | 15 |
| 9.7 | Drug-Laboratory Test Interactions | 15 |
| 10 | CLINICAL PHARMACOLOGY..... | 16 |
| 10.1 | Mechanism of Action | 16 |
| 10.2 | Pharmacodynamics | 16 |
| 10.3 | Pharmacokinetics..... | 17 |
| 11 | STORAGE, STABILITY AND DISPOSAL..... | 20 |
| PART II: SCIENTIFIC INFORMATION | | 21 |
| 13 | PHARMACEUTICAL INFORMATION | 21 |
| 14 | CLINICAL TRIALS | 21 |
| 14.1 | Trial Design and Study Demographics | 21 |
| 14.2 | Study Results | 23 |
| 14.4 | Immunogenicity..... | 24 |
| 15 | MICROBIOLOGY..... | 24 |
| 16 | NON-CLINICAL TOXICOLOGY..... | 25 |
| PATIENT MEDICATION INFORMATION | | 30 |

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AGRYLIN (anagrelide hydrochloride capsules) is indicated for:

- Treatment of patients with thrombocytopenia secondary to myeloproliferative neoplasms to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms, including thrombo-hemorrhagic events.

AGRYLIN is intended for chronic usage and has not been evaluated for treatment of the acute life threatening complications of thrombocytosis.

1.1 Pediatrics

The safety and efficacy of AGRYLIN in patients under 16 years of age have not been established. Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

The safety and effectiveness of AGRYLIN have not been evaluated in studies specific to the elderly. Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredients, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Anagrelide is contraindicated in patients with severe hepatic impairment. Use of anagrelide in patients with severe hepatic impairment has not been studied. Anagrelide must be used with caution in patients with moderate hepatic impairment as exposure to anagrelide is increased 8-fold in such patients, (4 DOSAGE AND ADMINISTRATION; 10 CLINICAL PHARMACOLOGY; 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Cases of Torsades de pointes and Prinzmetal Angina have been reported post market (7 WARNINGS AND PRECAUTIONS, Cardiovascular)

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Treatment with AGRYLIN (anagrelide hydrochloride capsules) should be initiated under close medical supervision. The recommended starting dosage of AGRYLIN is 0.5mg qid or 1mg bid, which should be maintained for at least one week. Dosage should then be adjusted to the lowest effective dosage required to reduce and maintain platelet count below 600,000/ μ L, and ideally to the normal range. The dosage should be increased by not more than 0.5mg/day in any one week. Dosage should not exceed 10mg/day or 2.5mg in a single dose (7 WARNINGS AND PRECAUTIONS, Monitoring Laboratory Tests). The decision to treat asymptomatic young adults with thrombocythemia secondary to myeloproliferative neoplasms should be individualized.

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 and regular monitoring of cardiovascular effects and hepatic toxicity. 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 (2 CONTRAINDICATIONS).

The observed pharmacokinetic differences between the elderly and younger patients with ET would not be expected to require alteration of the recommended dosing regimen of AGRYLIN (10 CLINICAL PHARMACOLOGY, Special Populations and Conditions – Geriatrics).

To monitor the effect of AGRYLIN 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 \leq 600,000/mcL, ranged from 4 to 12 weeks. Most patients will experience an adequate response at a dose of 1.5 to 3.0mg/day. Patients with known or suspected heart disease, renal insufficiency, or hepatic dysfunction should be monitored closely.

Discontinuation

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 four days and return to baseline levels in one to two weeks, possibly rebounding above baseline values. Therefore, platelets should be monitored frequently.

4.4 Administration

Agrilyn is taken orally, as directed by the healthcare professional.

4.5 Missed Dose

In the event of a missed dose at the beginning of your treatment, the patient should contact their healthcare professional.

In the event that a dose is missed during long-term treatment, the missed dose should be taken as soon as possible, unless it is almost time for the next dose. The missed dose should be skipped if it is almost time for the next regular dose. Two doses should not be taken at the same time.

5 OVERDOSAGE

Acute Toxicity and Symptoms

At higher than recommended doses, AGRYLIN has been shown to cause reductions in blood pressure, with occasional hypotension. There have been a small number of post-marketing case reports of intentional overdose with AGRYLIN (anagrelide hydrochloride capsules). Reported symptoms include sinus tachycardia and vomiting. Symptoms resolved with conservative management. Platelet reduction from AGRYLIN therapy is dose related; therefore, thrombocytopenia, which can potentially cause bleeding, is expected from overdose. Should overdose occur, cardiac, and central nervous system toxicity can also be expected.

Management and Treatment

In case of overdose, 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|-------------------------|------------------------------------|---------------------------|
|-------------------------|------------------------------------|---------------------------|

| | | |
|------|-----------------|---|
| oral | capsules 0.5 mg | Black iron oxide, crospovidone, gelatine, lactose anhydrous, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, silicone dioxide, sodium lauryl sulfate, titanium dioxide |
|------|-----------------|---|

AGRYLIN (anagrelide hydrochloride capsules) is available in capsules containing 0.5mg of anagrelide as anagrelide hydrochloride for oral administration.

AGRYLIN 0.5mg capsules: White, opaque capsules imprinted with “S” and “063” in black ink and supplied in bottles of 100.

Each capsule of AGRYLIN (anagrelide hydrochloride capsules) contains 0.5mg of anagrelide as anagrelide hydrochloride and the following non-medicinal ingredients:

- Black iron oxide, crospovidone, gelatine, lactose anhydrous, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, silicone dioxide, sodium lauryl sulfate, titanium dioxide.

7 WARNINGS AND PRECAUTIONS

General

The decision to treat asymptomatic young adults with thrombocytopenia secondary to myeloproliferative neoplasms should be individualized.

Sudden discontinuation or interruption of AGRYLIN (anagrelide hydrochloride capsules) treatment is followed by an increase in platelet count. Following discontinuation, an increase in platelet count can be observed within four days.

Carcinogenesis and Mutagenesis

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

Anagrelide produced no detectable or reproducible increases in gene mutational activity in studies conducted in vitro with mutant strains of *Salmonella typhimurium* in the Ames test, or in a mouse lymphoma mutagenesis assay, with or without a rat hepatic drug metabolising enzyme system.

In addition, no clastogenic activity was seen in vitro using cultured human peripheral lymphocytes or in vivo in a mouse bone marrow erythrocyte micronucleus assay. At the concentrations and doses employed in these studies, there was no indication that anagrelide

was a potential mutagen either directly or after metabolic activation.

Cardiovascular

Due to the positive inotropic and chronotropic effects and cardiovascular side-effects (8 ADVERSE REACTIONS) of AGRYLIN, it 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 (including investigations such as echocardiograph, electrocardiogram) is recommended for all patients, along with careful monitoring during treatment and further investigations carried out as necessary. In humans, therapeutic doses of AGRYLIN may cause cardiovascular effects, including vasodilation, tachycardia, palpitations, Prinzmetal angina 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 (10 CLINICAL PHARMACOLOGY, Pharmacodynamics – Effects on Heart Rate and QTc Interval).

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 hypokalemia, as cases of Torsades de pointes have been reported post market.

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 (10 CLINICAL PHARMACOLOGY, Special Populations and Conditions) or use with CYP1A2 inhibitors (9 Drug-Drug Interactions).

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.

Driving and Operating Machinery

Caution should be used when driving vehicles or machinery.

Hematologic

Use of concomitant AGRYLIN and acetylsalicylic acid has been associated with major hemorrhagic events (9 Drug-Drug Interactions).

Hepatic/Biliary/Pancreatic

Hepatic metabolism represents the major route of anagrelide clearance and liver function may therefore be expected to influence this process. AGRYLIN has not been studied in patients with

severe hepatic impairment and is contraindicated (2 CONTRAINDICATIONS). Exposure to anagrelide is increased 8-fold in patients with moderate hepatic impairment (4 DOSAGE AND ADMINISTRATION; 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions – Hepatic Insufficiency). It is recommended that patients with mild and moderate hepatic impairment receive AGRYLIN only if, in the physician's judgment, the potential benefits of therapy outweigh the potential risks. Patients with mild or moderate hepatic impairment should be carefully and regularly monitored for cardiovascular effects and hepatic toxicity while receiving AGRYLIN (7 WARNINGS AND PRECAUTIONS, Cardiovascular, and Adverse Reactions). In patients with moderate hepatic impairment, a dosage reduction is required (4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Monitoring and Laboratory Tests

AGRYLIN therapy requires close clinical supervision of the patient. To monitor the effect of AGRYLIN 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 $\leq 600,000/\text{mL}$, ranged from 4 to 12 weeks. Most patients will experience an adequate response at a dose of 1.5 to 3.0mg/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 four days and return to baseline levels in one to two weeks, possibly rebounding above baseline values. Therefore, platelets should be monitored frequently.

In patients with hepatic insufficiency or renal insufficiency, liver function and kidney function tests should be performed at least once per month or when deemed necessary in the physician's judgment (4 DOSAGE AND ADMINISTRATION). Electrolytes (potassium, magnesium and calcium) should also be monitored.

As cases of hepatitis have been reported from post-marketing surveillance, it is recommended that liver functions (ALT and AST) tests are performed before anagrelide treatment is initiated and at regular intervals thereafter (7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 4 DOSAGE AND ADMINISTRATION; 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Renal

It is recommended that patients with renal insufficiency (creatinine $\geq 2\text{mg/dL}$) receive AGRYLIN 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 AGRYLIN (8 ADVERSE REACTIONS).

Respiratory

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 associated with lung infiltrations. The time of onset ranges from 1 week to several years after initiating anagrelide. In most cases, the symptoms improved after discontinuation of anagrelide (8 ADVERSE REACTIONS, Post-Market Adverse Reactions).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. AGRYLIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

AGRYLIN 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 AGRYLIN. AGRYLIN may cause fetal harm when administered to a pregnant woman. In female pregnant rats administered AGRYLIN, implantation losses, reduction in fetal body weights and fetal survival were observed at doses in excess of the therapeutic range (16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breast-feeding

It is not known whether this drug is excreted in human milk; however, excretion of anagrelide-related material into milk has been demonstrated in rats (10 CLINICAL PHARMACOLOGY, Pharmacokinetics). Because many drugs are excreted in human milk and because of the potential for serious adverse reaction in nursing infants from AGRYLIN, 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.

7.1.3 Pediatrics

Pediatrics (<16 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

The safety and effectiveness of AGRYLIN have not been evaluated in studies specific to the elderly. Pharmacokinetic (PK) differences between elderly and younger patients with essential thrombocythemia (ET) have been observed (10 CLINICAL PHARMACOLOGY, Special Populations

and Conditions – Geriatrics; Dosage and Administration).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Serious adverse reactions were reported among 942 patients diagnosed with myeloproliferative neoplasms of varying etiology (Essential Thrombocythemia (ET): 551; Polycythemia Vera (PV): 117; other myeloproliferative neoplasms (OMPN): 274]). While most reported adverse events during AGRYLIN (anagrelide hydrochloride capsules) therapy have been mild in intensity and have decreased in frequency with continued therapy, serious adverse events included: 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.

The mean duration of AGRYLIN therapy for ET, PV, Chronic Myelogenous Leukemia (CML) and OMPN patients was 65, 67, 40 and 44 weeks, respectively. Of the 942 patients treated with AGRYLIN, 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 AGRYLIN.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse reaction data was obtained from three clinical trials involving 942 patients with myeloproliferative neoplasms treated with anagrelide.

The most frequently reported adverse reactions to AGRYLIN (in 5% or greater of 942 patients with myeloproliferative neoplasm) in clinical trials are included in Table 2.

| Table 2: Adverse events with an incidence of ≥5% | |
|---|----------------------------------|
| | AGRYLIN |
| Body as a Whole | Headache (43.5%) |
| | Asthenia (23.1%) |
| | Abdominal pain (16.5%) |
| | Pain, other (15.0%) |
| | Fever (8.9%) |
| | Chest pain (8.0%) |
| | Malaise (6.4%) |
| | Back pain (5.9%) |
| Cardiovascular | Palpitations (26.1%) |
| | Tachycardia (7.5%) |
| Digestive | Diarrhea (25.7%) |
| | Nausea (17.1%) |
| | Flatulence (10.2%) |
| | Vomiting (9.7%) |
| | Anorexia (7.7%) |
| | Dyspepsia (5.2%) |
| Metabolic | Edema, other (20.6%) |
| | Peripheral edema (8.5%) |
| Nervous | Dizziness (15.4%) |
| | Paresthesia (5.9%) |
| Respiratory | Dyspnea (11.9%) |
| | Pharyngitis (6.8%) |
| | Cough (6.3%) |
| Skin and Appendages | Pruritus (5.5%) |
| | Rash, including urticaria (8.3%) |

8.3 Less Common Clinical Trial Adverse Reactions

| Table 3: Adverse events with an incidence of 1% to <5% | |
|--|---|
| | AGRYLIN |
| Body as a Whole | Accidental injury, cellulitis, chills, flu symptoms, infection, neck pain, photosensitivity. |
| Cardiovascular | Angina pectoris, arrhythmia, cardiovascular disease, congestive heart failure, heart failure, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, thrombosis, vasodilatation. |
| Digestive | Constipation, dry mouth, dysphagia, eructation, gastritis, GI distress, GI hemorrhage, melena, nausea and vomiting. |

| Table 3: Adverse events with an incidence of 1% to <5% | |
|--|---|
| | AGRYLIN |
| Hemic & Lymphatic | Anemia, ecchymosis, lymphadenoma, thrombocytopenia, Platelet counts below 100,000/ μ L occurred in 84 patients (ET: 35; PV: 9; OMPN: 40), reduction below 50,000/ μ L occurred in 44 patients (ET: 7; PV: 6; OMPN: 31) while on AGRYLIN therapy. Thrombocytopenia promptly recovered upon discontinuation of AGRYLIN. |
| Hepatic | Elevated liver enzymes were observed in 3 patients (ET: 2; OMPN: 1) during AGRYLIN therapy. |
| Musculoskeletal | Arthralgia, arthritis, bone pain, leg cramps, myalgia. |
| Nervous | Amnesia, confusion, depression, insomnia, nervousness, somnolence. |
| Nutritional Disorders | Dehydration, edema, weight gain, weight loss. |
| Respiratory | Asthma, bronchitis, epistaxis, pneumonia, respiratory disease, rhinitis, sinusitis. |
| Skin and Appendages | Alopecia, skin discoloration, skin disease, skin ulcer, sweating. |
| Special Senses | Abnormal vision, amblyopia, conjunctivitis, diplopia, ear disorder, eye disorder, tinnitus, visual field abnormality. |
| Urogenital | Dysuria, hematuria, nocturia, urinary frequency, urinary incontinence, urinary tract disorder, urinary tract infection. |

Renal abnormalities occurred in 15 patients (ET: 10; PV: 4; OMPN: 1). Six ET, 4 PV and 1 with OMPN experienced renal failure (approximately 1%) while on AGRYLIN treatment; in 4 cases, the renal failure was considered to be possibly related to AGRYLIN treatment. The remaining 11 were found to have pre-existing renal impairment and were successfully treated with AGRYLIN. Doses ranged from 1.5-6.0mg/day, with exposure periods of 2 to 12 months. No dose adjustment was required because of renal insufficiency.

Other adverse drug reactions seen in these or other clinical studies: hypoesthesia (common), pulmonary hypertension (uncommon), supraventricular tachycardia (uncommon), ventricular tachycardia (uncommon).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

The data on which the indication were originally approved is not available.

8.5 Post-Market Adverse Reactions

In individual case reports, a causal relationship has been established between acute pulmonary reactions (severe hypersensitivity pneumonia ‘allergic alveolitis’, pulmonary infiltrates/fibrosis, and dyspnea) and the use of anagrelide. AGRYLIN should be discontinued in patients showing acute pulmonary reactions. Cases of Torsades de pointes and Prinzmetal angina have been reported (7 WARNINGS AND PRECAUTIONS, Cardiovascular). Congestive heart failure, cardiomyopathy, myocardial infarction and tubulointerstitial nephritis have occurred in a small number of patients with the use of anagrelide. Hepatitis has also been reported in patients who have taken anagrelide treatment. The incidence of these events is not known.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase (PDE) III. The effects of medicinal products with similar properties, such as the inotrope milrinone, may be exacerbated by anagrelide.

9.4 Drug-Drug Interactions

Limited pharmacokinetic (PK) and/or pharmacodynamic 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.

Apart from acetylsalicylic acid discussed further below, additional drug interaction studies have not been conducted, with the other most common medications used concomitantly with AGRYLIN (anagrelide hydrochloride) in clinical trials, which were acetaminophen, furosemide, iron, ranitidine, hydroxyurea, and allopurinol. The most frequently used concomitant cardiac medication has been digoxin. There is no clinical evidence to suggest that AGRYLIN interacts with any of these compounds.

Anagrelide is metabolized at least in part by CYP1A2. It is known that CYP1A2 is inhibited by several medicinal products, including fluvoxamine and ciprofloxacin, and such medicinal products could theoretically adversely influence the clearance of anagrelide and its active metabolite BCH24426. 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. In vivo experiments in animals and in vitro tests suggested that 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. Drug-drug interactions with CYP1A2 substrates and inhibitors cannot be excluded.

There is a single case report which suggests that sucralfate may interfere with AGRYLIN absorption.

Two clinical interaction studies in healthy subjects, a single-dose study of co-administered anagrelide 1mg and acetylsalicylic acid 900mg and a repeat-dose study of co-administered anagrelide 1mg once daily and acetylsalicylic acid 75mg once daily, demonstrated greater ex vivo anti-platelet aggregation effects than administration of acetylsalicylic acid alone. In the repeat-dose study, anagrelide alone had no effect on platelet aggregation, but did slightly enhance the inhibition of platelet aggregation by acetylsalicylic acid. There was a short-lived decrease in platelet aggregation beyond the effects of acetylsalicylic acid alone for the first 2 hours after administration. The clinical relevance of this interaction in essential thrombocythemia patients is unknown.

Co-administered anagrelide 1mg and acetylsalicylic acid 900mg single-dose was generally well tolerated. There was no effect on bleeding time, prothrombin time (PT) or activated partial thromboplastin time (aPTT). No clinically relevant pharmacokinetic interactions between anagrelide and acetylsalicylic acid were observed. In that same study, acetylsalicylic acid alone produced a marked inhibition in platelet aggregation ex vivo.

At therapeutic doses, anagrelide may potentiate the effects of other medicinal products that inhibit platelet aggregation. In some essential thrombocythemia patients concomitantly treated with acetylsalicylic acid and anagrelide, major haemorrhages occurred. Therefore, the potential risks and benefits of the concomitant use of anagrelide with acetylsalicylic acid should be assessed, particularly in patients with a high risk profile for haemorrhage and/or with a platelet count greater than $1000 \times 10^9/L$ before treatment is commenced.

9.5 Drug-Food Interactions

Food decreased the C_{max} of anagrelide by 14%, but increased the $AUC_{0-\infty}$ by 20%. For both parameters, the exposure after food was not equivalent to that in the fasted state. Food decreased the C_{max} of the active metabolite BCH24426 by 29%, but had no effect on the $AUC_{0-\infty}$. The most marked effects of food were evident in a longer time lag before absorption (or appearance, in the case of BCH24426), a slower rate of absorption and a later time of peak for plasma concentration of both anagrelide and BCH24426.

Grapefruit juice has been shown to inhibit CYP1A2 and therefore could also reduce the clearance of anagrelide.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism by which AGRYLIN (anagrelide hydrochloride capsules) 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 was shown to inhibit PDE III found in platelets and as a result raises cAMP levels, which in turn may explain the inhibitory effect on platelet aggregation. Platelet aggregation is inhibited in humans at doses higher than those required to reduce platelet count. Two major metabolites, one active and one inactive, have been identified. The active metabolite, BCH24426 or 3-hydroxy anagrelide, shows similar potency and efficacy as anagrelide in the platelet lowering effect. Exposure as measured by plasma AUC is approximately 2-fold higher for 3-hydroxy anagrelide (BCH24426) compared to anagrelide. The inactive metabolite, RL603 or 5,6-dichloro-3,4-dihydroquinazolin-2-ylamine, does not participate in the overall effect of AGRYLIN.

10.2 Pharmacodynamics

Oral administration of single and multiple doses of anagrelide in healthy volunteers caused dose related reductions in platelet count during treatment. In addition, dose-related reductions occur in platelet aggregation. These effects were reversible following cessation of treatment. No clinically important changes in other study variables were noted, i.e., bleeding time, platelet survival time, bone marrow morphology, blood pressure, pulse rate, urinalysis, and EKG. Anagrelide is well tolerated at low doses. A 5mg dose caused orthostatic hypotension and dizziness in healthy volunteers; doses of 1 to 2mg/day were tolerable.

In most cases, the incidence of adverse effects is dose-related, intensity is mild, duration is transient, and treatment is unnecessary.

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

Pharmacological evaluation of anagrelide and its metabolites showed that 3-hydroxy anagrelide (BCH24426) had a comparable inhibitory effect to the parent drug on megakaryocytopoiesis – and therefore platelet formation – while RL603 was inactive. Anagrelide and 3-hydroxy anagrelide (BCH24426) were also found to be inhibitors of PDEIII although 3-hydroxy anagrelide (BCH24426) was almost forty times more potent than the parent drug while RL603 was again

virtually inactive.

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.

10.3 Pharmacokinetics

Absorption

Single oral-dose administration of either 1 or 2mg of anagrelide resulted in C_{max} values ranging between 7 and 13ng/mL, about 1 hour after administration.

Pharmacokinetic data obtained from healthy subjects comparing the pharmacokinetics of anagrelide in the fed and fasted states showed that administration of a 1mg dose of anagrelide with food decreased the C_{max} by 14%, but increased the AUC by 20%. For both parameters, the exposure after food was not equivalent to that in the fasted state. Food decreased the C_{max} of the active metabolite BCH24426 by 29%, but had no effect on the $AUC_{0-\infty}$. The most marked effects of food were evident in a longer time lag before absorption (or appearance, in the case of BCH24426), a slower rate of absorption and a later time of peak for plasma concentration of both anagrelide and BCH24426.

Distribution

The available plasma concentration time data at the steady state in patients showed no evidence of anagrelide accumulation in plasma after repeated administration. Long term oral administration (≥ 2 months to >5 years) of anagrelide at doses of 2 to 4mg/day resulted in plasma levels within the range expected after a single dose.

Metabolism

The drug is extensively metabolized; less than 1% is recovered in the urine as anagrelide. At fasting and at a dose of 0.5mg of anagrelide, the plasma half-life is 1.3 hours.

Elimination

In humans, 61% of the administered radioactivity was excreted in the 24 hours following administration and over 90% had been excreted by 72 hours after administration. Following oral administration of ^{14}C -anagrelide in humans, 79% of the radioactivity was recovered in urine and 21% was recovered in the feces. Urinary excretion was monophasic, while the plasma half life of anagrelide was in the range of 1 to 2 hours. This pharmacokinetic half-life is consistent with the clinical dose frequency of 2 to 4 times per day. The plasma half-life of the pharmacologically active metabolite, 3-hydroxy anagrelide (BCH24426), was approximately 3 hours. The data indicate that all radioactivity was recovered in the urine and feces within 168 hours (7 days) of oral administration.

There was a statistically greater amount of anagrelide metabolite excreted in the urine during the 24-hour period after fasted administration of anagrelide, compared to after the fed state. These differences, however, were not considered to be clinically significant.

Long-term oral administration (≥ 2 months to >5 years) of anagrelide at doses of 2 to 4mg/day resulted in mean excretion values for the major metabolite in the 24-hour urine sample similar to those values obtained following single oral-dose administration of 0.5mg of anagrelide.

Special Populations and Conditions

- **Pediatrics**

An open-label study conducted in 17 pediatric patients 7 to 14 years of age and 18 adult patients (67% of which were elderly patients, i.e., 65 years of age and older) with essential thrombocythemia indicated that dose and body weight-normalized exposure, C_{\max} and AUC of anagrelide were lower in children/adolescents compared to adults (C_{\max} 48%, AUC_t 55%).

| Table 4. Summary of PK Parameters for Anagrelide and Metabolite in Adolescent/Adult and Pediatric/Adolescent Subjects on 0.5mg bid Regimen | | | | |
|---|-------------------------------|---------------------------------|-------------------------------|---------------------------------|
| PK Parameter | Anagrelide | | BCH24426 | |
| | AA (n=4) Mean (SD) | PA (n=4-6) Mean (SD) | AA (n=4) Mean (SD) | PA (n=4-6) Mean (SD) |
| T_{max} (h) | 1.9 (1.5) | 3.9 (3.1) | 2.4 (1.1) | 4.0 (3.1) |
| C_{max} (ng/mL) | 3.1 (1.3) | 1.9 (0.6) | 4.5 (1.8) | 5.5 (2.8) |
| C_{min} (ng/mL) | 0 | 0.03 (0.04) | 0.2 (0.1) | 0.4 (0.2) |
| AUC (ng.h/mL) | 8.6 (3.3) | 8.2 (3.3) | 19.9 (3.7) | 24.4 (8.3) |
| $T_{1/2z}$ (h) | 1.5 (0.5) | 3.9 (3.7) | 2.8 (0.7) | 4.2 (1.6) |
| C_{avg} (ng/mL) | 0.7 (0.3) | 0.7 (0.3) | 1.7 (0.3) | 2.0 (1.7) |
| FI | 4.3 (1.0) | 3.2 (2.2) | 2.5 (0.6) | 1.1 (0.9) |
| Cl/F (mL/min) | 1062 (315) | 1169 (465) | 429 (71) | 1004 (455) |

AA: Adolescent/adult subject group; PA: Pediatric/adolescent subject group.

- **Geriatrics**

Pharmacokinetic data from fasting elderly patients with ET (age range 65 to 75 years) compared to fasting adult patients (age range 22 to 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 caused by lower presystemic metabolism of anagrelide to 3-hydroxy anagrelide in the elderly patients.

- **Hepatic Insufficiency**

Hepatic metabolism represents the major route of anagrelide clearance and liver function is expected to influence this process. Accordingly, an open label pharmacokinetic study has been performed on subjects with moderate hepatic impairment (and otherwise healthy) vs. healthy subjects. A single dose of 1mg anagrelide was administered to each individual. Though a limited number of patients were enrolled for the study, the results show that $AUC_{0-\infty}$ was nearly 8 times higher in subjects with moderate hepatic impairment (n=10) than in healthy subjects (n=10). A strong correlation has been established between the AUC measurements and the Child-Pugh Score (indicator of hepatic impairment severity). Pharmacokinetic measurements performed on 3-hydroxy anagrelide (BCH24426, the active metabolite of anagrelide) and RL603 (the inactive metabolite of anagrelide) show approximately a doubling of AUC in patients with moderate hepatic impairment as compared to healthy subjects. No study has been performed either on patients with severe

or on patients with mild hepatic impairment, therefore, no data are available.

11 STORAGE, STABILITY AND DISPOSAL

Store from 15°C to 25°C in a light-resistant container.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

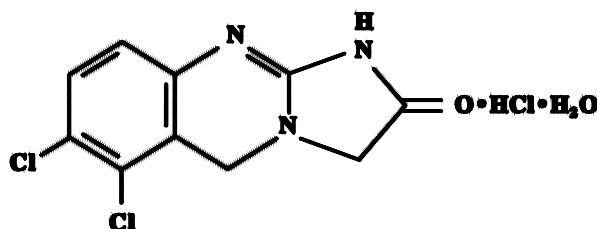
Drug Substance

Proper name: anagrelide hydrochloride

Chemical name: 6,7-dichloro-1,5-dihydroimidazo[2,-1-*b*]-quinazolin-2(3H)-one monohydrochloride monohydrate

Molecular formula and molecular mass: C₁₀H₇Cl₂N₃O•HCl•H₂O 310.55

Structural formula:



Physicochemical properties:

Anagrelide hydrochloride is an off-white, non-volatile powder. It is practically insoluble in water and very slightly soluble in dimethyl sulfoxide and dimethylformamide.

In aqueous solutions at 25°C, the solubility of anagrelide below pH 3 increased as the pH was decreased. The solubility at pH 0.96 was 236µg/mL. Between pH 4 and pH 8, the solubility remained constant at 1.2µg/mL. Above pH 8, the solubility increased with increasing pH consistent with ionization of the quinazoline moiety. The solubility at pH 11.4 was 992µg/mL.

The estimated pKa values were 2.9 and 9.8 and the melting point was above 300°C.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

A total of 942 patients with myeloproliferative neoplasms 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 neoplasms (OMPN), were treated with anagrelide in three clinical trials. Patients with OMPN included 87 patients who had Myeloid Metaplasia with Myelofibrosis (MMM), and 9 patients who had unknown myeloproliferative neoplasms.

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

ET

- Platelet count $\geq 900,000$ mL 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 $\geq 50,000$ /mL, without evidence of infection
- Absolute basophil count ≥ 100 /mL
- Evidence for hyperplasia of the granulocytic line in the bone marrow
- Philadelphia chromosome present
- Leucocyte alkaline phosphatase \leq lower limit of the laboratory normal range

PV[†]

- A1 Increased red cell mass
- A2 Normal arterial oxygen saturation
- A3 Splenomegaly
- B1 Platelet count $\geq 400,000$ /mL, in absence of iron deficiency or bleeding
- B2 Leucocytosis ($\geq 12,000$ /mL, in the absence of infection)
- B3 Elevated leucocyte alkaline phosphatase
- B4 Elevated serum B₁₂

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

MMM

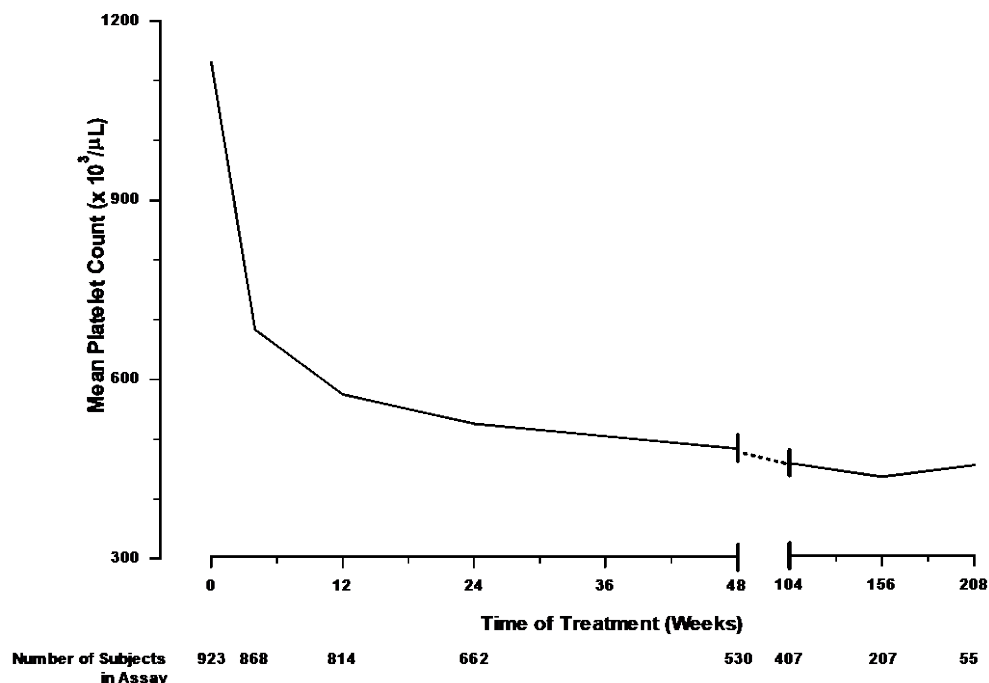
- Myelofibrotic (hypocellular, fibrotic) bone marrow
- Prominent megakaryocytic metaplasia in bone marrow
- Splenomegaly
- Moderate to severe normochromic normocytic anemia
- White cell count may be variable; (80,000-100,000/mL)
- Increased platelet count
- Variable red cell mass; teardrop poikilocytes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

14.2 Study Results

The parameters used to determine the efficacy of anagrelide in the treatment of patients with thrombocythemia secondary to myeloproliferative neoplasms showed a clinically significant improvement over time of treatment. Anagrelide was shown to be an efficacious treatment for patients with thrombocytosis, decreasing the platelet count and the incidence of symptoms associated with a high platelet count. It is also effective in patients who have failed on or been intolerant of other anti-thrombocytotic therapy. Unlike other agents used to treat thrombocytosis, the action of anagrelide is specific to platelets and overall has no clinical effect on the plasma level of other formed elements in the blood.

Patients were enrolled in clinical trials if their platelet count was $\geq 900,000/\text{mCL}$ on two occasions or $\geq 650,000/\text{mCL}$ on two occasions with documentation of symptoms associated with thrombocythemia. The mean duration of anagrelide therapy for ET, PV, CML, and OMPN 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 0.5-2.0mg every 6 hours. The dose was increased if the platelet count was still high, but to no more than 12mg 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 $\leq 600,000/\mu\text{L}$, 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 Neoplasms
Mean Platelet Count During Anagrelide Therapy**



| | Time on Treatment | | | | | | | |
|-------|-------------------|-------|-----|-----|-----|-------|-----|-----|
| | Baseline | Weeks | | | | Years | | |
| | | 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 10³/µL

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

14.4 Immunogenicity

The data on which the indication were originally approved is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Acute oral doses of anagrelide as high as 2,500mg/kg in mice and 1,500mg/kg in the rat, caused decreased activity immediately after administration; all animals recovered within 1 to 2 days. Intraperitoneal administration of 500mg/kg of anagrelide to mice, resulted in the death of all animals within 3 days, while administration of 250mg/kg caused decreased activity with recovery by 2 days.

In dogs, diarrhea was observed 4 to 5 days after a single oral dose of 10mg/kg of anagrelide and after 1 to 2 days with doses of ≥ 50 mg/kg. Emesis was also observed, 2 days after a dose of 100mg/kg and on the day of dosing with doses of ≥ 500 mg/kg; all animals recovered.

Single oral doses of 200mg/kg of anagrelide in rhesus monkeys caused soft stools and a transient decrease in food consumption after 3 days; all animals recovered.

These results indicate that the acute oral LD₅₀ is $>2,500$ mg/kg in mice, $>1,500$ mg/kg in the rat, >800 mg/kg in dogs, and >200 mg/kg in primates (rhesus monkey).

Long-Term Toxicity

Anagrelide was administered daily to rats by oral gavage for 27 days at doses of 50 to 1,000mg/kg/day. Findings included flushing of the ears, feet, and nose. Drug-related changes seen at 1,000mg/kg/day consisted of decreased platelet counts, retarded body weight gains in males, and mild fibrosis and myocarditis along with labored respiration and/or rales; one female died. In a 94-day study, administration of 4 to 12mg/kg/day of anagrelide resulted in dose-related intestinal tract lesions and increased liver, adrenal, and thyroid weights relative to body weight at the highest dose.

Administration of escalating oral doses up to 3,200mg/kg over a period of 7 days in dogs resulted in a decrease in food consumption, in females at doses as low as 100mg/kg, and in males at doses as low as 800mg/kg. Clinical signs of gastrointestinal upset were evident; all dogs exhibited loose stools, diarrhea, and ultimately vomited as the dose was increased. In a 28-day repeat-dose study in the dog, the only abnormalities reported with oral doses were diarrhea and vomiting at doses of 500 to 800mg/kg/day.

Multidose studies were performed in primates using oral doses of 10mg/kg/day for 14 days or 4 to 12mg/kg/day of anagrelide for up to 92 days of treatment. Clinical signs related to anagrelide treatment consisted of diarrhea, emesis, soft and/or loose stools and decreased food consumption.

Chronic toxicity studies were carried out for up to 12 months in rats and dogs. In the rat, doses of 120.5, 361.5, and 1,205mg/kg/day of anagrelide were administered orally by diet. Treatment-related findings included the following: hunched posture; dilated vagina in females; increases and decreases in body weight; increased food consumption; mild transient increases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), decreased platelet counts in females; changes in serum chemistry indicative of mild to moderate liver and

kidney damage in all groups; increased cholesterol, decreased triglycerides, decreased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in males, increased creatinine in males, marginal increases in basal urea nitrogen (BUN) and creatinine in females, increased urine volume; liver and kidneys in all treated rats and adrenals in males were significantly increased in weight relative to body weight and/or brain weight; focal hyperplasia at the highest dose and pheochromocytomas at doses ≥ 361.5 mg/kg/day. There were 24 deaths during the study (see Table 5); though none were attributed to anagrelide treatment, necropsy findings indicated kidney and liver damage.

| | Anagrelide (mg/kg/day) | | | |
|--|-------------------------------|--------|--------|--------|
| | 0 | 120.5 | 361.5 | 1,205 |
| Cause of Death * | | | | |
| Leukemia | | 1M | 1M | |
| Nephropathy | | 2M | | |
| Inflammation/infection and/or hemorrhage/thrombi | 1M | 2M | 2M | 2M; 1F |
| Heart failure | | | | 1M |
| Accident | | 1M | 1F | |
| Unknown | | 1F | 3M | 5M |
| Total | 1M | 6M; 1F | 6M; 1F | 8M; 1F |

* Animals may have had more than one finding at necropsy/histopathology

In the chronic dog toxicity study, repeated exposure to 10 to 600mg/kg/day of anagrelide were associated with a variety of toxicities, including: diarrhea and emesis; significant reductions in red cell counts, hemoglobin, hematocrit, and platelet counts; a tendency toward increased kidney weight in both sexes and increased liver weight in females; dose-related cardiac changes consisting of minimal to marked hemorrhage and chronic inflammation were present in the myocardium of the right atrium and left AV valves along with proliferative changes in some cardiac vessels.

Carcinogenicity

At the concentrations and doses employed in the non-clinical carcinogenicity studies, there was no indication that anagrelide was a potential mutagen either directly or after metabolic activation (7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

Reproductive and Developmental Toxicology

A comprehensive range of fertility, embryofetal development, and pre- and post-natal toxicity studies were performed in rats at oral doses of 30 to 900mg/kg/day of anagrelide.

In a fertility and early embryofetal development study in which female rats were dosed for 15 days prior to pairing, during pairing and up to and including Day 6 of gestation, an increase in the incidences of both pre- and post-implantation losses, leading to a decrease in the mean

number of embryos per female was observed at 30mg/kg/day. The No Observed Effect Level (NOEL) was considered to be 10mg/kg/day. These data are consistent with an earlier study assessing fertility in rats which showed evidence of reduced implantations and increased resorptions at all doses tested (60, 120 and 240mg/kg/day).

In the embryofetal development and pre- and post-natal studies, females were dosed from Days 6 to 15 or 18 of gestation, Day 6 gestation through Day 7 lactation, or Day 15 gestation to Day 21 lactation. The average number of live pups was significantly reduced on Day 1 postpartum in the 60 and 120mg/kg/day dosage groups; Days 4 and 21 postpartum in the 120 and 240mg/kg/day dosage groups and Day 7 postpartum in the 120mg/kg/day dosage group. Average body weights of pups were significantly reduced in all anagrelide-treated groups at Day 1 postpartum; in the 120 and 240mg/kg/day groups on Days 4 and 7 postpartum, and in the 240mg/kg/day group on Day 14 postpartum. Administration of anagrelide did not adversely affect the averages for implantations and live litter sizes, number of dams with all stillbirths, number of dams with all pups dying during lactation, sex ratios, or clinical and necropsy observations of the pups.

Doses of 240mg/kg/day and higher were associated with an increase in the incidence of pups dying on Days 1 to 4 postpartum, a decrease in the percentage of pups surviving to Day 7 postpartum, and a decrease in the average pup weight/litter.

Fetal body weights were significantly reduced by 5 to 7% in groups receiving 300 and 900mg/kg/day. Significant reversible delays in fetal ossification occurred in groups given doses of 100mg/kg/day or higher. No fetal malformations were attributable to doses of anagrelide as high as 900mg/kg/day. Deaths occurred when rats were continued to be dosed during delivery and early lactation.

In embryofetal development studies with rabbits, oral doses of 30 to 480mg/kg of anagrelide, administered from Days 6 to 18 of gestation revealed that doses of ≥ 60 mg/kg/day caused body weight loss, severe decreases in food consumption, decreased live litter sizes, and increased number and percentages of resorptions per litter. Deaths occurred in all dosed groups and there were two deformed fetuses, one at 30 and another at 240mg/kg/day. A second study of similar design employed doses of 1 to 20mg/kg/day. Body weight gains were significantly increased with 10 or 20mg/kg/day while food consumption significantly decreased during dosing. There were no deaths, abortions, premature deliveries, changes in litter parameters, or fetal malformations with oral doses of ≤ 20 mg/kg/day.

DETAILED PHARMACOLOGY

Clinically, AGRYLIN (anagrelide hydrochloride capsules) was found to be an effective, highly specific platelet-reducing agent. Anagrelide's effects on platelets are fully reversible. Moreover, it has no clinically significant effect on the other formed elements in the blood. These findings were demonstrated both preclinically and clinically.

Preclinical pharmacology data that are available demonstrate anagrelide's specificity toward platelets. While anagrelide was found to be a potent inhibitor of platelet aggregation, it had no significant effect on other cellular components of the blood. Additional significant pharmacologic effects attributed to anagrelide administration are hypotension and positive

inotropic activity.

Mechanism of Action

Anagrelide is a highly selective platelet-lowering agent. In vitro studies of human megakaryocytopoiesis suggested that, in vivo, its thrombocytopenic activity results primarily from an inhibitory effect on the post-mitotic phase of megakaryotic maturation. Anagrelide inhibited thrombopoietin-induced megakaryocytopoiesis in a dose-dependent manner with an estimated IC₅₀ of approximately 30nM (= 7.7ng/mL), consistent with the in vivo C_{max} of 7-13ng/mL after doses of 0.5-1mg. Three in vivo studies in humans (published in abstract form) have confirmed that anagrelide decreases circulating platelet counts in thrombocythemic subjects by inhibiting megakaryocyte maturation and ploidy.

Effect on Platelet Count

An effect on platelet count was demonstrated in only a few animal studies. In one rat study, a decreased platelet count was found in male Sprague-Dawley rats treated at 1,000mg/kg for 27 days. In another rat study, decreased platelet counts were observed in all female rats dosed for 1 year with 120.5, 361.5, and 1,205mg/kg/day of anagrelide hydrochloride. Platelet counts were decreased from pre-study values by 30 to 54% in male beagle dogs, and by 23 to 40% in females treated for 1 year at doses of 10, 300, and 600mg/kg/day.

Anti-thrombotic Studies

The ability of anagrelide to inhibit thrombosis was demonstrated in four different animal models: rat, rabbit, dog, and rhesus monkey. Anagrelide was found to be a potent, broad-spectrum platelet aggregation inhibitor whose effects are dose-related. It is 50 times more potent than acetylsalicylic acid as an anticoagulant and was found to have a synergistic effect on platelet aggregation inhibition when administered in conjunction with heparin.

Cardiovascular Pharmacology

Preclinical cardiovascular information was obtained during the course of studies conducted in four different animal models: rat, guinea pig, ferret, and dog.

The key findings in these studies was that anagrelide has a significant direct positive inotropic effect and direct vasodilatory effect; and causes dose-related decreases in mean blood pressure and reflexogenic increases in heart rate. Anagrelide was also shown to be a potent vasodilator and cardiotonic agent in dogs. All of these effects were seen at doses higher than the recommended clinical dose of 2.0mg/day.

General Pharmacology Studies

General pharmacologic effects of anagrelide were studied in five different animal models: rat, guinea pig, ferret, rabbit, and dog. The overall conclusions from these studies were that anagrelide causes the following:

- simple competitive antagonism of peripheral 5-HT receptors in the rat fundus model
- a decrease in diuresis sodium and chlorine excretion in the volume-loaded normotensive rat

- a dose-related prolongation of bleeding time in the guinea pig extracorporeal shunt model
- no behavioural or neurological changes in the conscious dog model
- weak airway dilation in the anesthetized dog model
- inhibition of both cyclic AMP (cAMP) phosphodiesterase (PDE) and cyclic GMP PDE activity in a study of supernatant and sonicate models
- inhibition of cAMP PDE activity in another study of supernatant and sonicate models
- an increase in cAMP level and cAMP-dependent protein kinase (cA-PK) ratio in the washed human platelet model
- inhibition of platelet PDE and resultant elevation of cAMP in the intact platelet model

Pharmacokinetics

Studies on the absorption, distribution, metabolism, and excretion (ADME) in four different species (rat, dog, monkey, and human) revealed that the orally-administered anagrelide is generally well absorbed, widely distributed to tissues, extensively metabolized, and excreted in the urine.

In a study with pregnant or post-partum female rats administered ¹⁴C-labelled anagrelide, anagrelide-related material was partitioned into milk and was still being secreted in milk at the final sampling time of 24 hours.

The monkey most closely resembled man in the route, rate, and extent of excretion. Human and animal urinary metabolite profiles were qualitatively similar. Each of the 3 main metabolites present in human urine were present in animal urine, but quantities were generally smaller.

Oral administration of ¹⁴C-labelled anagrelide in the monkey resulted in rapid absorption with peak plasma levels occurring 4 to 8 hours after dosing. Capsule dose absorption from the intestinal tract was 76%. The main route of elimination was the urine; by 6 days after drug administration, the mean cumulative urinary excretion level of the dosed radioactivity was 61%.

A secondary route of elimination was in feces, the mean cumulative fecal excretion level over 6 days after drug administration was 31% in monkeys. The amount of parent compound detected in the urine as unchanged drug was less than 3%. Bioavailability in the primate was 92%, with a terminal half-life of 2 days for total radioactivity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE



anagrelide hydrochloride capsules

Read this carefully before you start taking **AGRYLIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AGRYLIN**.

Serious Warnings and Precautions

The following serious heart problems have been reported in people taking AGRYLIN:

- **Torsades de pointes (life-threatening irregular heart rhythm):** dizziness, fainting, heart palpitations, chest pain, rapid heartbeat, shortness of breath, cold sweats, nausea
- **Prinzmetal Angina:** painful spasm of the blood vessels on the heart (while resting, usually at night or in the early morning)

If you have any of the symptoms listed above while you are taking AGRYLIN tell your healthcare professional immediately.

What is AGRYLIN used for?

- AGRYLIN is used in patients 16 years of age and older with thrombocythemia caused by myeloproliferative neoplasms. Thrombocythemia is a condition in which there are too many platelets (the little cells which help the blood to clot) in the blood. Myeloproliferative neoplasms are diseases in which one or more of the types of cells that make up the blood are being overproduced.
- Lowering platelet counts improves symptoms, including serious symptoms related to blockages in blood vessels and bleeding.

How does AGRYLIN work?

The way that AGRYLIN works in the body to reduce your platelet count is not fully understood. AGRYLIN is believed to reduce the number of platelets by affecting megakaryocytes (the cells that produce platelets). Its action slows down platelet production.

Although AGRYLIN lowers platelet counts to more normal levels, it does not affect the body's natural process to clot blood when needed.

What are the ingredients in AGRYLIN?

Medicinal ingredients: anagrelide hydrochloride

Non-medicinal ingredients: Black iron oxide, crospovidone, gelatine, lactose anhydrous, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, silicone dioxide, sodium lauryl sulphate, titanium dioxide.

AGRYLIN comes in the following dosage forms:

Capsule; 0.5mg

Do not use AGRYLIN if you:

- Have severe liver disease
- Are allergic to anagrelide or any of the other nonmedicinal ingredients (see What are the ingredients in AGRYLIN) in AGRYLIN or its container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AGRYLIN. Talk about any health conditions or problems you may have, including if you:

- were born with or have family history of prolonged QT interval (seen on ECG, electrical recording of the heart), or you are taking other medicines that result in abnormal ECG changes or if you have low levels of electrolytes in your blood e.g., potassium, magnesium or calcium
- have heart, lung, liver or kidney disease
- are pregnant or planning a pregnancy
- are breast feeding

Other warnings you should know about:

AGRYLIN and ASA: Use of AGRYLIN with acetylsalicylic acid (ASA) has been associated with a risk of major bleeding events. Tell your healthcare professional if you are taking ASA. Also tell your healthcare professional if you have an increased risk of bleeding. Before starting treatment, your healthcare professional will consider the potential risks and benefits of using AGRYLIN with ASA.

Pregnancy and Breastfeeding:

- AGRYLIN is not recommended in women who are or may become pregnant.
- AGRYLIN can harm your unborn baby. You should not get pregnant while you are taking AGRYLIN. Your healthcare professional will do a test to make sure you are not pregnant before you start taking AGRYLIN.
- You must use an effective form of birth control while you are taking AGRYLIN. If you think you might be pregnant tell your healthcare professional immediately.

- Talk to your healthcare professional if you are breastfeeding or planning to breastfeed. You should not breastfeed while you are taking AGRYLIN as it can cause serious side effects in your baby.

Blood Tests: AGRYLIN can cause abnormal blood tests results. Your healthcare professional will do blood tests before you start treatment and while you are taking AGRYLIN to closely monitor your platelet levels and to see how well your liver and kidneys are working.

Driving and Using Machines: Caution should be used when driving vehicles or machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AGRYLIN:

- medicines that can alter your heart rhythm
- acetylsalicylic acid (ASA), used for pain and fever
- fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) used to treat depression
- ciprofloxacin, an antibiotic used to treat bacterial infections
- omeprazole, used to treat stomach problems such as ulcers and acid reflux
- theophylline, used to treat breathing problems such as COPD and asthma
- milrinone, used to treat heart failure
- sucralfate, used to treat ulcers

Grapefruit juice may also interact with AGRYLIN.

How to take AGRYLIN:

- Take as directed by your healthcare professional.

Usual dose (16 years of age and older):

Starting dose: 2 mg daily, taken as either 0.5 mg 4 times a day or 1 mg twice a day.

Your healthcare professional will slowly increase your dose until the right dose is found.

Overdose:

If you think you, or a person you are caring for, have taken too much AGRYLIN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Possible symptoms of an overdose of AGRYLIN could include low levels of platelets in your blood, which can cause bleeding and low blood pressure.

Missed Dose:

If you miss a dose at the beginning of your treatment, tell your healthcare professional.

If you miss a dose during your long-term treatment, take the missed dose as soon as possible, unless it is almost time for your next dose. Skip the missed dose if it is almost time for your next regular dose. Do not take two doses at the same time.

What are possible side effects from using AGRYLIN?

These are not all the possible side effects you may have when taking AGRYLIN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

Abdominal pain, back pain, cough, digestive problems, headache, diarrhea, fatigue, fever, gas, loss of appetite, malaise, nausea, pain, redness and itching of skin, sore throat, tingling, vomiting, dizziness.

You may also experience: bruises, chills, constipation, dry mouth, ear problems (ringing in the ear), flushing, flu symptoms, hair loss, infection, infection of the sinuses, insomnia (trouble sleeping), muscle and bone pain, neck pain, nervousness, breathing problems, changes in weight, skin problems, sweating.

| Serious side effects and what to do about them | | | |
|--|---|---------------------|--|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| VERY COMMON | | | |
| Chest pain | | √ | |
| Palpitations: pounding or irregular heartbeat | | √ | |
| Edema: swelling in your feet or ankles | | √ | |
| Trouble breathing or shortness of breath | | | √ |
| COMMON | | | |
| Bleeding | | √ | |
| Blood in your stools or urine | | √ | |
| Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch, sudden chest pain, difficulty breathing, heart palpitations | | | √ |
| Confusion | | √ | |
| Dehydration | | √ | |

| Serious side effects and what to do about them | | | |
|---|--------------------------------------|--------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| Depression: inability to concentrate, low mood | | √ | |
| Asthma: difficulty breathing | | √ | |
| Difficulty swallowing | | √ | |
| Fast or irregular heartbeat | | √ | |
| Respiratory infection (pneumonia or bronchitis): fever, cough, chest pain, shortness of breath | | √ | |
| High blood pressure | | √ | |
| Hypoesthesia: decreased or loss of feeling or sensation such as numbness | | √ | |
| Irritation or infection of the eye | √ | | |
| Loss of consciousness | | | √ |
| Loss of memory | | √ | |
| Low blood pressure: lightheaded, dizzy, shortness of breath or fainting; may occur when you go from lying or sitting to standing up | | √ | |
| Nose bleeding | | √ | |
| Heart disease or heart failure: swollen legs or ankles or difficulty breathing | | | √ |
| Trouble with vision | | √ | |
| Urinary problems | | √ | |
| RARE | | | |
| Supraventricular tachycardia, Ventricular tachycardia : irregular and abnormally fast heart beat | | | √ |
| Pulmonary hypertension: shortness of breath, swelling in legs or ankles or lips, skin can turn bluish colour | | | √ |
| FREQUENCY NOT KNOWN | | | |
| Allergic lung conditions: coughing, severe trouble | | | √ |

| Serious side effects and what to do about them | | | |
|--|--------------------------------------|--------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| breathing, shortness of breath, fever, chills, body aches | | | |
| Liver problems: nausea, vomiting, loss of appetite, yellowing of the skin or eyes, dark urine, unusual tiredness | | √ | |
| Kidney problems: decreased urination, nausea, vomiting, swelling of extremities, fatigue | | √ | |
| Torsades de pointes (life-threatening irregular heart rhythm): dizziness, fainting, heart palpitations, chest pain, rapid heartbeat, shortness of breath, cold sweats, nausea | | | √ |
| Prinzmetal angina: painful spasm of the blood vessels on the heart (while resting, usually at night or early morning) | | | √ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store from 15°C to 25°C in a light-resistant container.

Keep out of reach and sight of children.

If you want more information about AGRYLIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (www.takeda.com/en-ca/agrylinpm), or by calling 1-800-268-2772.

This leaflet was prepared by

Takeda Canada Inc.

22 Adelaide Street West, Suite 3800

Toronto, Ontario M5H 4E3

Last Revised: JUL 07, 2021

AGRYLIN® is a registered trademark of Takeda Pharmaceuticals U.S.A., Inc.

TAKEDA™ and the TAKEDA Logo® are trademarks of Takeda Pharmaceutical Company Limited, used under license.