AUSTRALIAN PRODUCT INFORMATION

AGRYLIN® (Anagrelide hydrochloride) capsules

1 NAME OF THE MEDICINE

Anagrelide hydrochloride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AGRYLIN capsules is available in the following strength: 0.5 mg. Each capsule of AGRYLIN contains 0.5 mg of anagrelide base (as anagrelide hydrochloride).

AGRYLIN (anagrelide hydrochloride) is an orally active quinazoline derivative.

Excipient(s) with known effect
Contains sugars as lactose.

Each capsule contains lactose monohydrate (53.7 mg) and lactose (65.8 mg).
For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Capsule.

AGRYLIN is available as 0.5 mg white opaque capsule, containing white powder and printed with Shire logo "S" on the cap and "063" on the body in blank ink (AUST R 71752).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AGRYLIN capsules are indicated for the treatment of essential thrombocythaemia.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with AGRYLIN capsules should be initiated under close medical supervision. The recommended starting dosage of AGRYLIN for adult patients is 1 mg /day, which should be administered orally in two divided doses (0.5 mg/dose). The starting dose should be maintained for at least a week. The dose should then be adjusted to the lowest effective dose required to reduce and maintain 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 should be increased by not more than 0.5 mg/day in any one week. Dosage should not exceed 10 mg/day or 2.5 mg in a single dose because of the hypotensive effect of anagrelide (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

The decision to treat asymptomatic young adults with essential thrombocythaemia should be individualised (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hepatic impairment
For patients with moderate hepatic impairment, the recommended starting dose is 0.5 mg/day, to be maintained for a minimum of one week with close monitoring of cardiovascular effects. AGRYLIN is not recommended for patients with severe hepatic impairment.

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

Typically, platelet count begins to respond within 7 to 14 days at the proper dosage. Most patients will experience an adequate response at a dose of 1.5 to 3.0 mg/day. Patients with known or suspected heart disease, renal insufficiency, or hepatic dysfunction should be monitored closely. Where immediate reduction of the platelet count is required, pheresis may be a more appropriate therapeutic intervention (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.3 CONTRAINDICATIONS

AGRYLIN is contraindicated in patients who have developed hypersensitivity to anagrelide hydrochloride or any of its excipients (see Section 6.1 LIST OF EXCIPIENTS) and in patients with severe hepatic impairment. Exposure to anagrelide is increased 8-fold in patients with moderate hepatic impairment. Use of anagrelide in patients with severe hepatic impairment has not been studied.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Cardiovascular
Therapeutic doses of anagrelide may cause cardiovascular effects, including vasodilation, tachycardia, palpitations and congestive cardiac failure. A pre-treatment cardiovascular examination (including investigations such as echocardiography, electrocardiogram) is recommended for all patients. Patients should be monitored during treatment of cardiovascular effects and further investigations carried out as necessary. Hypokalaemia or hypomagnesaemia must be corrected prior to anagrelide administration. Anagrelide should be used with caution in patients with known or suspected heart disease or at high risk of vascular events, and only if the potential benefits of therapy outweigh the potential risks (see also Patient monitoring/Effects of laboratory tests in this section).

Anagrelide has been shown to increase both the heart rate and QTc interval in healthy volunteers. The clinical impact of this effect is unknown (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

Bleeding

Use of concomitant anagrelide and aspirin (acetylsalicylic acid) has been associated with major haemorrhagic events (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in renal impairment

Patients with renal impairment (serum creatinine ≥ 0.18 mmol/L) should be monitored closely since they are at greater risk of renal toxicity while receiving anagrelide (see Section 4.8 ADVERSE EFFECTS/Urogenital System).

Use in hepatic impairment

Exposure to anagrelide is increased 8-fold in patients with moderate hepatic impairment. Use of anagrelide in patients with severe hepatic impairment has not been studied. The potential risks and benefits of anagrelide therapy in a patient with mild or moderate impairment of hepatic function should be assessed before and during treatment is commenced. In patients with moderate hepatic impairment, dose reduction is required, and patients should be carefully monitored for cardiovascular effects (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION for specific dosing recommendations).

Patients with hepatic impairment (serum bilirubin, AST or other measures of hepatic function > 1.5 times the upper limit of normal) should be monitored closely while receiving anagrelide since anagrelide may worsen hepatic impairment (see Section 4.8 ADVERSE EFFECTS/Hepatic System).

Patient monitoring/Effects on laboratory tests

Anagrelide therapy requires close clinical supervision of the patient. While the platelet count is being lowered (usually during the first two weeks of treatment), platelet count should be performed every 2 days during the first week of treatment and at least weekly thereafter until the maintenance dosage is reached (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). As cases of hepatitis have been reported from post-marketing surveillance, it is recommended that liver function tests (ALT and AST) are performed before anagrelide treatment is initiated and at regular intervals thereafter. A full blood count (haemoglobin, white blood cells and platelet count), renal function (serum creatinine, urea) tests and electrolytes (potassium, magnesium and calcium) should continue to be monitored during anagrelide therapy. Patients should be regularly assessed during anagrelide therapy for the emergence of cardiovascular effects which may require further examination and

investigation. The QTc interval should be closely monitored during anagrelide treatment.

Paediatric use

The efficacy and safety of anagrelide in patients under the age of 16 years have not been established.

Use in the elderly

The observed pharmacokinetic differences between elderly and young patients with essential thrombocythemia (ET) do not warrant using a different starting regimen or different dose titration step to achieve an individual patient-optimised anagrelide regimen.

Cessation of AGRYLIN treatment

In general, interruption of anagrelide treatment is followed by an increase in platelet count. After sudden stoppage of anagrelide therapy, the increase in platelet count can be observed within four days. It should be noted that there is risk of thromboembolic events during this rebound phase. The dynamics of the rise in platelet count following interruption of therapy have been studied in only a very small number of patients, and data from normal controls suggests that a rebound to beyond pre-treatment levels occurs in some individuals. Therefore, platelet count should be monitored frequently.

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Patients should be advised how to recognise early signs and symptoms suggestive of thrombotic complications, such as cerebral infarction, and if symptoms occur to seek medical assistance.

Treatment discontinuation

In the event of dosage interruption or treatment withdrawal, platelets should be monitored frequently (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Limited PK and/or PD studies investigating possible interactions between anagrelide and other medicinal products have been conducted.

Warfarin or digoxin

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.

Aspirin (acetylsalicylic acid) and drugs that increase bleeding risk

At therapeutic doses, anagrelide may potentiate the effects of other medicinal products that inhibit platelet aggregation. 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 anti-platelet aggregation effects than administration of aspirin alone. Co-administered anagrelide 1 mg and aspirin 900 mg

single-doses had no effect on bleeding time, prothrombin time (PT) or activated partial thromboplastin time (aPTT). In the repeat-dose study, there was a short-lived decrease in *ex vivo* collagen- induced platelet aggregation beyond the effects of aspirin alone for the first 2 hours after administration. In some ET patients concomitantly treated with aspirin and anagrelide, major haemorrhages have occurred. 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 commenced.

Other PDE3 inhibitors

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III (PDE3). The effects of drugs with similar properties such as inotropes (e.g. milrinone) may be exacerbated by anagrelide.

CYP1A2 inhibitors

Anagrelide is primarily metabolised 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, thereby increasing plasma concentrations. Anagrelide demonstrated inhibitory activity towards CYP1A2 *in vitro* which presents a theoretical potential for interaction with other co-administered medicinal products sharing that clearance mechanism e.g. theophylline.

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.

Preclinical data indicate an augmented anticoagulant effect when heparin and anagrelide were used in combination.

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

Food has no clinically significant effect on the bioavailability of anagrelide.

Although additional drug interaction studies have not been conducted, the most common medications used concomitantly with anagrelide in clinical trials have been aspirin, paracetamol, frusemide, iron, ranitidine, hydroxyurea, and allopurinol. The most frequently used concomitant cardiac medication has been digoxin. Other than aspirin, there is no clinical evidence to suggest that anagrelide interacts with any of these compounds.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies in animals have shown reproductive toxicity. Anagrelide hydrochloride at oral doses up to 240 mg/kg/day (1,440 mg/m^2/day, 195 times the maximum recommended human dose based on body surface area) had no effect on fertility of male rats. However, in female rats, given oral doses of 60 mg/kg/day (360 mg/m^2/day, 49 times the maximum recommended human dose based on body surface area) or higher, it disrupted implantation when administered in early pregnancy. A no-effect dose level was not established.

Use in pregnancy

Australian Pregnancy Categorisation (Category B3)

Anagrelide is not recommended in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the foetus. Women of child-bearing potential should be instructed that they must not be pregnant and that they should use contraception while taking anagrelide. Anagrelide may cause foetal harm when administered to a pregnant woman. There are no adequate studies of anagrelide use in pregnant women.

Five women became pregnant while on anagrelide treatment at doses of 1 to 4 mg/day. Treatment was stopped as soon as it was realised they were pregnant. All delivered normal, healthy babies.

No teratogenic effects were observed in pregnant rats at oral doses up to 900 mg/kg/day (5400 mg/m^2/day, 730 times the maximum recommended human dose based on body surface area), or in pregnant rabbits at oral doses up to 20 mg/kg/day (240 mg/m^2/day, 32 times the maximum recommended human dose based on body surface area). However, increased embryonic deaths and suppression of foetal growth were seen in rats at oral doses of 60 mg/kg/day (360 mg/m^2/day, 49 times the maximum recommended human dose based on body surface area) or greater, and ossification was retarded at 100 mg/kg/day or greater. When administered to rats in late pregnancy at oral doses of 60 mg/kg/day or higher, it retarded or blocked parturition, resulting in maternal and neonatal deaths.

Use in lactation

It is not known whether this drug is excreted in human milk. When administered to lactating rats, anagrelide hydrochloride at doses greater than 60 mg/kg/day (360 mg/m^2/day, 49 times the maximum recommended human dose based on body surface area) decreased survival of the offspring. Because many drugs are excreted in human milk and in view of the unknown risks of anagrelide to the infant, a decision to discontinue nursing or to discontinue the drug should be seriously considered, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

AGRYLIN may cause dizziness in some patients. Caution should be shown when driving or operating machinery whilst on treatment with AGRYLIN.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

While most reported adverse events during anagrelide therapy have been mild in intensity and have decreased in frequency with continued therapy, serious adverse events reported in patients with ET and/or in patients with thrombocythaemias or other aetiologies include: congestive heart failure, myocardial infarction, cardiomyopathy, cardiomegaly, complete heart block, atrial fibrillation, torsades de pointes, ventricular tachycardia, cerebrovascular accident, pericarditis, pericardial effusion, pleural effusion, pulmonary infiltrates, pulmonary fibrosis, pulmonary hypertension, pancreatitis, hepatitis, gastric/duodenal ulceration, tubulointerstitial nephritis and seizure.

Of the 551 patients treated with anagrelide for a mean duration of 65 weeks, 82 (15%) were discontinued from the study because of adverse events or abnormal laboratory test results. The most common adverse events for treatment discontinuation were headache, diarrhoea, oedema, palpitation and abdominal pain. Overall, the occurrence rate of all adverse events

was 17.9 per 1,000 treatment days. The occurrence rate of adverse events increased at higher dosages of anagrelide.

Adverse reactions arising from clinical studies, post-authorisation 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). (Italic text denotes post-marketing ADRs).

<u>General disorders and administration site conditions</u>

Very common:	Headache (44.5%), asthenia (22.1%), pain, other than abdominal, chest or back (14.7%).
Common:	Fever, Influenza-like illness, chills, neck pain, photosensitivity, paraesthesia, back pain, malaise.
Uncommon:	Oedema, chest pain

<u>Cardiac and vascular disorders</u>

Very common:	Palpitations (27.2%), oedema (19.8%).
Common:	Arrhythmia, haemorrhage, cardiovascular disease, cerebrovascular accident, angina pectoris, congestive heart failure, hypertension, orthostatic hypotension, vasodilatation, chest pain, tachycardia, peripheral oedema.
Uncommon:	Ventricular tachycardia, supraventricular tachycardia, atrial fibrillation.
Rare:	Myocardial infarction, cardiomyopathy, cardiomegaly, pericardial effusion.
Not known:	**Torsade de pointes, Prinzmetal angina*

<u>Gastrointestinal disorders</u>

Very common:	Diarrhoea (24.3%), abdominal pain (17.4%), nausea (15.1%), flatulence (10.5%).
Common:	Constipation, GI distress, GI haemorrhage, gastritis, melena, aphthous stomatitis, eructation, nausea, vomiting, dyspepsia.
Uncommon:	Pancreatitis

<u>Blood & lymphatic system disorders</u>

Common:	Anaemia, thrombocytopenia, ecchymosis, lymphadenoma. Platelet counts below 100 x 10^9 /L occurred in 35 patients and reduction below 50 x 10^9 /L occurred in 7 of the 551 ET patients while on anagrelide therapy. Thrombocytopenia promptly recovered upon discontinuation of anagrelide.

<u>Hepatobiliary disorders</u>

Common:	Elevated liver enzymes.
Not known:	**Hepatitis*

<u>Musculoskeletal and connective tissue disorders</u>

Common:	Arthralgia, myalgia, leg cramps.
Uncommon:	Back pain

<u>Nervous system disorders</u>

Very common:	Dizziness (14.5%), headache
Common:	Depression, hypoesthesia, somnolence, confusion, insomnia, nervousness, amnesia, migraine, syncope.
Uncommon:	Paraesthesia.
Not known:	Cerebral infarction

Psychiatric disorders

Uncommon:	Depression, confusional state, insomnia, nervousness

Metabolism and nutritional disorders

Common:	Dehydration, decreased appetite

Respiratory, thoracic and mediastinal disorders

Very common:	Dyspnoea (10.5%).
Common:	Rhinitis, epistaxis, respiratory disease, sinusitis, pneumonia, bronchitis, asthma, cough, pharyngitis.
Uncommon:	Pleural effusion, Pulmonary hypertension
Rare:	Lung infiltration
Not known:	**Interstitial lung disease including pneumonitis and allergic alveolitis*

Skin and subcutaneous tissue disorders

Common:	Pruritus, skin disease, alopecia, rash including urticaria.
Uncommon:	Ecchymosis

Eye, Ear and labyrinth disorders

Common:	Amblyopia, visual impairment, tinnitus, visual field abnormality, diplopia.

Renal and urinary disorders:

Common:	Dysuria, haematuria.
Rare:	Renal failure
Not known:	**Tubulointerstitial nephritis*

Investigations:

Uncommon:	Hepatic enzymes increased.

[*] *Italic text denotes post-marketing ADRs*

Of the 551 patients, 10 were found to have renal abnormalities. Six of the 10 experienced renal failure (approximately 1%) while on anagrelide treatment; in two, the renal failure was considered to be possibly related to anagrelide treatment. The remaining 4 were found to have pre-existing renal impairment and were successfully treated with anagrelide. Doses ranged from 1.5 - 6.0 mg/day, with exposure periods of 2 to 12 months. Serum creatinine remained within normal limits and no dose adjustment was required because of renal insufficiency.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Acute toxicity and symptoms

Symptoms of acute toxicity were decreased motor activity in mice and rats and softened stools and decreased appetite in monkeys.

At higher than recommended doses, anagrelide 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 anagrelide. Reported symptoms include sinus tachycardia and vomiting. Symptoms resolved with conservative 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.

Management and treatment

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

For information on the management of overdose, contact the Poisons Information Centre telephone: 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Healthy male volunteers given anagrelide demonstrated dose-related reductions in platelet counts. The reduction after 8-10 days treatment with anagrelide 0.5 mg bd was 24-30% and with 1 mg bd, 30-44%. After 1 mg mane for 30 days, the average reduction in platelet count was 15%. Platelet counts returned to normal within one week of ceasing treatment.

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.

Pharmacodynamic Effects

In vitro studies of the growth of human megakaryocyte colonies in tissue culture showed that anagrelide disrupted the postmitotic phase of megakaryocyte development reducing megakaryocyte size and ploidy. Anagrelide did not have a thrombocytopenic effect in the animal models tested, rats, dogs and monkeys, at doses ≤ 10 mg/kg/day.

Anagrelide at doses ≥ 1 mg inhibited ADP- and collagen-induced platelet aggregation in healthy volunteers. Anagrelide 0.5 mg twice daily for 14 days followed by anagrelide 1 mg twice daily for a further 14 days reduced haemoglobin concentration by a median 12 g/L. In *in vitro* studies of human blood, anagrelide inhibited cyclic AMP phosphodiesterase.

Anagrelide produces dose-dependent vasodilation, decreasing blood pressure and increasing heart rate and ventricular contractility. In a pharmacodynamic study, a dose of 5 mg caused orthostatic hypotension and dizziness in nine healthy volunteers (average fall in standing

blood pressure = 22/15 mmHg. Only minimal changes in blood pressure were observed following a dose of 2 mg.

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, randomised, placebo- and active-controlled, cross-over study in 60 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 (upper 2-sided 90% CI 8.0 msec) occurring at 2 hours for 0.5 mg and +10.0 msec (upper 2-sided 90% CI 12.7 msec) occurring at 1 hour for 2.5 mg. Anagrelide exposure was higher in women than men (C_{max} 55-75% higher; AUC 90% higher) and women had higher heart rate changes (and QTc changes) than men around the time of T_{max}.

Note: The recommended starting dosage of AGRYLIN is 0.5 mg twice daily and should be increased by not more than 0.5 mg/day in any one week (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

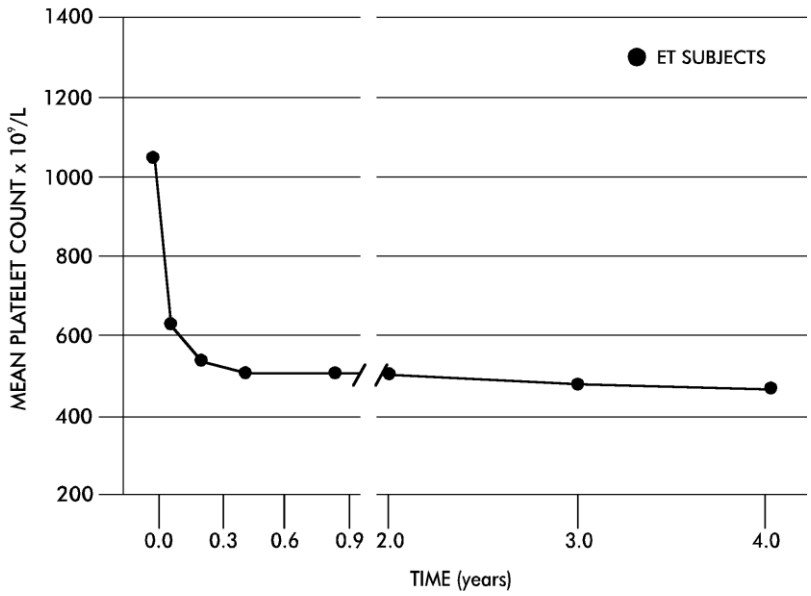
Clinical trials

A total of 551 patients with essential thrombocythaemia (ET) were treated with anagrelide in two uncontrolled trials and in compassionate use. Patients with ET were diagnosed based on the following criteria:

- Platelet count $\geq 900 \times 10^9$/L 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.

The mean duration of anagrelide therapy for study patients was 65 weeks; 23% of patients received treatment for 2 years. In the main trial, 274 ET 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. The criteria for defining subjects as "responders" were reduction in platelets for at least 4 weeks to $\leq 600 \times 10^9$/L, or by at least 50% from baseline value. Subjects treated for less than 4 weeks were not considered evaluable. 79% of evaluable patients (n=254) responded and 73% of patients receiving at least one dose (n=274) responded. The reduction in mean platelet count is depicted graphically below:

Least Square Means for Platelet Count during Anagrelide Therapy



Time on Treatment								
	Baseline	**Weeks**				**Years**		
		4	**12**	**24**	**48**	**2**	**3**	**4**
Mean*	1045	627	537	506	508	501	474	464
N	274**	265	245	206	179	139	76	11

* x 10^9/L

** Two hundred seventy-six ET subjects were enrolled in this study. There is no anagrelide information available for two of those subjects. Therefore, 274 subjects represent the intent-to-treat population who received anagrelide therapy.

In an investigator-led randomised controlled trial, patients with ET who were at high risk of vascular events were randomized to either anagrelide + aspirin (n=405) or hydroxyurea + aspirin (n=404). Use of anagrelide monotherapy was not studied. Patients were high risk if they had one or more of the following: age ≥ 60 years, current or previous platelet count > 1,000 x 10^9/L, history of ischaemia, thrombosis, embolism, haemorrhage caused by ET, hypertension requiring therapy or diabetes requiring a hypoglycaemic agent. The initial anagrelide dose was 0.5 mg twice daily and the initial hydroxyurea dose 0.5 to 1 g daily. The dose was then adjusted to maintain platelet count < 400 x 10^9/L. The aspirin dose was 75-100 mg per day. Median follow up was 39 months (range 12-72).

Both groups achieved similar control of platelet count within 9 months of trial entry. Anagrelide + aspirin were associated with a significantly higher incidence of arterial thrombosis (9.1% vs 4.2%), serious haemorrhage (5.4% vs 2.0%) and transformation to myelofibrosis (4.0% vs 1.2%) in this high-risk group compared to hydroxyurea + aspirin. Rates of death, from any cause, were not significantly different between the two groups.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Single oral doses of 1-2 mg anagrelide are absorbed rapidly in healthy male volunteers, mean

t_{max} being 0.9 h. Following administration of ^{14}C-anagrelide in people, more than 70% of radioactivity was recovered in urine. Based on limited data, there appears to be a trend toward dose linearity between doses of 0.5 mg and 2.0 mg. At fasting and at a dose of 0.5 mg of anagrelide, the plasma half-life is 1.3 hours. The available plasma concentration time data at steady state in patients show that anagrelide does not accumulate in plasma after repeated administration. Anagrelide protein binding in human plasma is 91%.

Pharmacokinetic data obtained from healthy Caucasian 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%. Food also reduced the C_{max} of 3-hydroxy anagrelide.

Metabolism

The drug is extensively metabolised; less than 1% is recovered in the urine as anagrelide. Two major metabolites have been identified RL 603 and 3-hydroxy anagrelide. RL603 is considered pharmacologically inactive whilst 3-hydroxy anagrelide is pharmacologically active, being equipotent as the parent compound in terms of platelet inhibition and 40 times more potent as an inhibitor of phosphodiesterase III.

Excretion

The half-life of 3-hydroxy anagrelide is approximately 3 hours. Metabolites are excreted in urine (79%) and faeces (21%). Excretion is > 97% complete within 5 days. Anagrelide is metabolised by CYP1A2, and therefore there is potential for interaction with other co-administered drugs that alter (inhibit or induce) CYP1A2-mediated metabolism (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Special Populations Pharmacokinetics

Pharmacokinetic (PK) data from paediatric (age range 7-14 years) and adult (age range 16-86 years) patients with thrombocythaemia secondary to a myeloproliferative disorder (MPD), indicate that dose and body weight-normalised exposure, C_{max} and AUC_t, of anagrelide were lower in the paediatric patients compared to the adult patients (C_{max} 48%, AUC_t 55%).

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

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 pre-systemic 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. The pharmacokinetic results show that the exposure to 3-hydroxy anagrelide is higher (100% increase in plasma elimination half-life from 3 to 6 hours) in severe renally impaired patients although the C_{max} did not differ.

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Anagrelide did not cause gene mutations in bacterial or mammalian cells, nor was it clastogenic in the human lymphocyte chromosome aberration test *in vitro* or the mouse micronucleus test *in vivo*.

Carcinogenicity
In a two year rat carcinogenicity study a higher incidence of uterine adenocarcinoma, was observed in females receiving 30 mg/kg/day (99 times human AUC for anagrelide and 18 times human AUC for metabolite 3-hydroxyanagrelide) with a NOEL of 10 mg/kg/day (6 times human AUC for anagrelide and twice human AUC exposure for metabolite 3-hydroxyanagrelide after the maximum recommended clinical dose of 10 mg/day). Adrenal phaeochromocytomas were increased in males receiving 3 mg/kg/day and above, and in females receiving 10 mg/kg/day and above. A NOEL was not established in males and for females was 3 mg/kg/day (1.6 times human AUC exposure to anagrelide and less than the human exposure to metabolite 3-hydroxyanagrelide after the maximum recommended clinical dose of 10 mg/day). Adrenal phaeochromocytomas were also found in a one-year rat study.

No long-term data in humans are available to evaluate the carcinogenic potential of anagrelide hydrochloride. The maximum duration of human exposure in clinical trials was 4 years.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each capsule of AGRYLIN contains the following non-medicinal ingredients: crospovidone, lactose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and povidone.

For active ingredient, refer to Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 INCOMPATIBILITIES

Please refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

AGRYLIN capsules are available in bottles of 100 capsules.

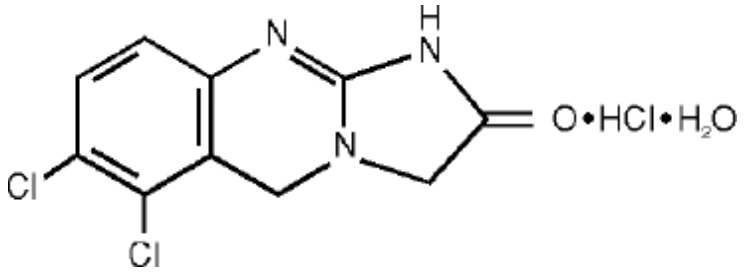
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical Structure



CAS number

The CAS Registry Number for anagrelide hydrochloride is 58579-51-4.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only Medicine (S4).

8 SPONSOR

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Telephone: 1800 012 612
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9 DATE OF FIRST APPROVAL

16 February 2000

10 DATE OF REVISION

19 September 2022

Summary table of changes

Section Changed	Summary of new information
4.4	Added statement under 'Cardiovascular' 2 new subsections added: 'Bleeding' and 'Treatment discontinuation' Added statement under 'Thrombotic risk'
4.5	Added statement added under 'Aspirin (Acetylsalicylic Acid) and Drugs that Increase Bleeding Risk'
4.6	Added statement under 'Effects on fertility'
4.8	New ADR under 'Nervous System disorders' Changed frequency for 'Hypesthesia' Post-marketing ADRs identified