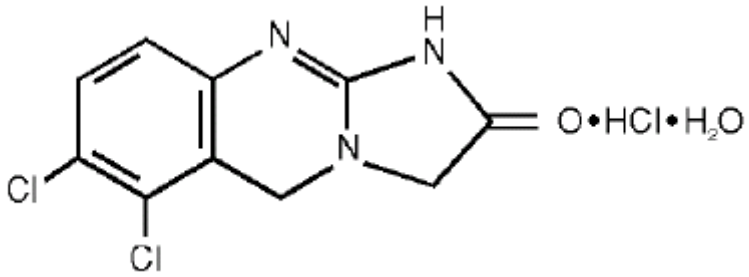
PRODUCT INFORMATION

Agrylin®

NAME OF THE MEDICINE

Anagrelide hydrochloride



DESCRIPTION

Agrylin (anagrelide hydrochloride) is an orally active quinazolin derivative. The CAS Registry Number for anagrelide hydrochloride is 58579-51-4.

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

Each capsule of Agrylin contains 0.5 mg of anagrelide base (as anagrelide hydrochloride) and the following non-medicinal ingredients: crospovidone, lactose anhydrous, lactose monohydrate, magnesium stearate, microcrystalline cellulose and povidone.

PHARMACOLOGY

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.

The mechanism by which anagrelide reduces blood platelet count is still under investigation. *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 (Cmax 55-75% higher; AUC 90% higher) and women had higher heart rate changes (and QTc changes) than men around the time of Tmax.

Note: The recommended starting dosage of Agrylin is 0.5mg twice daily and should be increased by not more than 0.5 mg/day in any one week (see DOSAGE and ADMINISTRATION).

Pharmacokinetic Properties

Single oral doses of 1-2 mg anagrelide are absorbed rapidly in healthy male volunteers, mean t_{max} being 0.9h. Following administration of 14C-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%. The drug is extensively metabolised; less than 1% is recovered in the urine as anagrelide. The pharmacological activity of the metabolites is unknown. 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. 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 are also mainly metabolised by CYP1A2 (see "Interactions with other drugs").

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.

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 presystemic metabolism of anagrelide to 3-hydroxy anagrelide in the elderly patients.

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

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

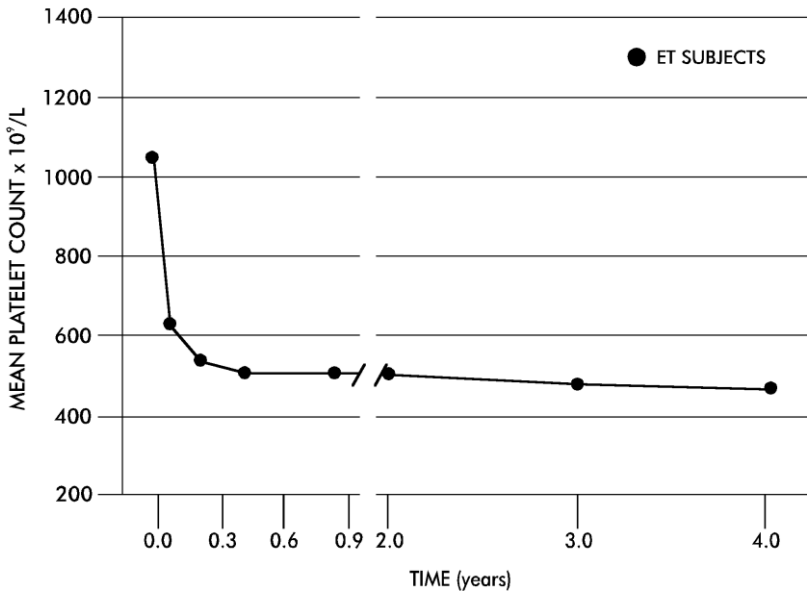
CLINICAL TRIALS

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							
		Weeks				Years		
	Baseline	**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.

INDICATIONS

Agrylin Capsules are indicated for the treatment of essential thrombocythaemia.

CONTRAINDICATIONS

Agrylin is contraindicated in patients who have developed hypersensitivity to anagrelide hydrochloride or any of its excipients (see DESCRIPTION) 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.

PRECAUTIONS

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. 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).

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 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 (Cmax) of anagrelide or its active metabolite, 3-hydroxy-anagrelide, e.g. hepatic impairment or use with CYP1A2 inhibitors (see Interactions with Other Drugs).

Renal

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

Hepatic

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 treatment is commenced. In patients with moderate hepatic impairment, dose reduction is required and patients should be carefully monitored for cardiovascular effects (see DOSAGE and ADMINISTRATION for specific dosing recommendations).

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 ADVERSE EFFECTS, Hepatic System).

Patient Monitoring

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 DOSAGE and 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 platelets), 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.

Effects on Fertility

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 (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 fetus. Women of child-bearing potential should be instructed that they must not be pregnant and that they should use contraception while taking anagrelide. Anagrelide may cause fetal harm when administered to a pregnant woman. 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 fetal 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.

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 ET do not warrant using a different starting regimen or different dose titration step to achieve an individual patient-optimised anagrelide regimen.

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.

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*.

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 pretreatment levels occurs in some individuals.

Driving and Operating Machinery

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

Interaction with Other Drugs

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

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

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

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. 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.

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.

ADVERSE 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.

The very common (≥ 10%), common (1% to < 10%) and uncommon (0.1% to <1%) adverse events to anagrelide of 551 patients with ET in clinical trials were:

Body as a Whole System:

Very common:	Headache (44.5%), asthenia (22.1%), pain, other than abdominal, chest or back (14.7%).
Common:	Fever, flu symptoms, chills, neck pain, photosensitivity, paraesthesia, back pain, malaise.

Cardiovascular System:

Very common:	Palpitations (27.2%), oedema (19.8%).
Common:	Arrhythmia, haemorrhage, cardiovascular disease, cerebrovascular accident, angina pectoris, heart failure, hypertension, postural hypotension, vasodilatation, migraine, syncope, chest pain, tachycardia, peripheral oedema.
Uncommon:	Supraventricular tachycardia

Digestive System:

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.

Haemic & Lymphatic System:

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.

Hepatic System:

Common:	Elevated liver enzymes.

Musculoskeletal System:

Common:	Arthralgia, myalgia, leg cramps.

Nervous System:

Very common:	Dizziness (14.5%).
Common:	Depression, somnolence, confusion, insomnia, nervousness, amnesia.
Uncommon:	hypoaesthesia

Nutritional Disorders:

Common:	Dehydration, anorexia.

Respiratory System:

Very common:	Dyspnoea (10.5%).
Common:	Rhinitis, epistaxis, respiratory disease, sinusitis, pneumonia, bronchitis, asthma, cough, pharyngitis.

Skin and Appendages System:

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

Special Senses:

Common:	Amblyopia, abnormal vision, tinnitus, visual field abnormality, diplopia.

Urogenital System:
Common: Dysuria, haematuria.

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 creatinines remained within normal limits and no dose adjustment was required because of renal insufficiency.

In addition to the cardiovascular adverse events described above, ventricular tachycardia has been reported as an uncommon adverse reaction (0.1% to < 1%) in individual case reports and clinical trials.

Pulmonary hypertension has been reported as an uncommon adverse reaction (0.1% to <1%) in clinical trials.

Allergic alveolitis, including interstitial lung disease and pneumonitis associated with the use of anagrelide have been reported in individual case reports. However, no case reports have occurred during clinical trials, post-marketing studies, or compassionate use programmes, therefore, the incidence of these events is not known.

DOSAGE AND 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 150-400 x 10^9/L. The dose should be increased by not more than 0.5 mg/day in any one week.

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.

Dosage should not exceed 10 mg/day or 2.5 mg in a single dose because of the hypotensive effect of anagrelide (see Pharmacodynamic Properties). The decision to treat asymptomatic young adults with essential thrombocythaemia should be individualised.

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.

OVERDOSAGE

Acute Toxicity and Symptoms

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

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 advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

PRESENTATION

Agrylin is available as:
0.5 mg opaque, white capsules imprinted “S 063” in black ink (AUST R 71752).

STORAGE CONDITIONS

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Shire Australia Pty. Limited
Level 6
123 Epping Rd
North Ryde NSW 2113
Australia

POISON SCHEDULE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

16 February 2000

DATE OF MOST RECENT AMENDMENT

31 March 2017