1. NAME OF THE MEDICINAL PRODUCT

Agrylin 0.5mg hard capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 0.5 mg anagrelide (as anagrelide hydrochloride).

Excipient(s) with known effect:
Each hard capsule contains lactose monohydrate (53.7 mg) and anhydrous lactose (65.8 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

An opaque white hard capsule imprinted with S 063.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the treatment of patients with Essential Thrombocythemia to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms.

An at risk patient
An at risk essential thrombocythaemia patient is defined by one or more of the following features:

- > 60 years of age or
- a platelet count > 1000 x 10^9/l or
- a history of thrombo-haemorrhagic events.

4.2 Posology and method of administration

Treatment with Agrylin capsules should be initiated by a clinician with experience in the management of essential thrombocythaemia.

The recommended starting dose of anagrelide 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 one week. After one week the dose may be titrated, on an individual basis, to achieve the lowest effective dose required to reduce and/or maintain a platelet count below 600 x 10^9/l and ideally at levels between 150 x 10^9/l and 400 x 10^9/l. The dose increment must not exceed more than 0.5 mg/day in any one-week and the recommended maximum single dose should not exceed 2.5 mg (see section 4.9). During clinical development doses of 10 mg/day have been used.

The effects of treatment with anagrelide must be monitored on a regular basis (see section 4.4). If the starting dose is > 1 mg/day platelet counts should be performed every two days during the first week of treatment and at least weekly thereafter until a stable maintenance dose is reached. Typically, a fall in the platelet count will be observed within 14 to 21 days of

starting treatment and in most patients an adequate therapeutic response will be observed and maintained at a dose of 1 to 3 mg/day (for further information on the clinical effects refer to section 5.1).

Older people
The observed pharmacokinetic differences between older and young patients with ET (see section 5.2) do not warrant using a different starting regimen or different dose titration step to achieve an individual patient-optimised anagrelide regimen.

During clinical development approximately 50% of the patients treated with anagrelide were over 60 years of age and no age specific alterations in dose were required in these patients. However, as expected, patients in this age group had twice the incidence of serious adverse events (mainly cardiac).

Renal impairment
There are limited pharmacokinetic data for this patient population. The potential risks and benefits of anagrelide therapy in a patient with impairment of renal function should be assessed before treatment is commenced.

Hepatic impairment
There are limited pharmacokinetic data for this patient population. However, hepatic metabolism represents the major route of drug clearance and liver function may therefore be expected to influence this process. Therefore it is recommended that patients with moderate or severe hepatic impairment are not treated with anagrelide. The potential risks and benefits of anagrelide therapy in a patient with mild impairment of hepatic function should be assessed before treatment is commenced (see sections 4.3 and 4.4).

Paediatric population
The experience in children is limited; anagrelide should be used in this patient group with caution Currently available data are described in . sections 5.1 and 5.2 but no recommendation on a posology can be made.

4.3 Contraindications

Hypersensitivity to anagrelide or to any of the excipients listed in section 6.1.
Patients with moderate or severe hepatic impairment.
Patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min).

4.4 Special warnings and precautions for use

Hepatic impairment
The potential risks and benefits of anagrelide therapy in a patient with mild impairment of hepatic function should be assessed before treatment is commenced. It is not recommended in patients with elevated transaminases (> 5 times the upper limit of normal) (see sections 4.2 and 4.3).

Renal impairment
The potential risks and benefits of anagrelide therapy in a patient with impairment of renal function should be assessed before treatment is commenced (see sections 4.2 and 4.3).

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

Platelets
The platelet count will increase within 4 days of stopping treatment with Agrylin capsules and will return to pre-treatment levels within 10 to 14 days.

Cardiovascular
Serious cardiovascular adverse events including cases of torsade de pointes, ventricular tachycardia, cardiomyopathy, cardiomegaly and congestive heart failure have been reported (see section 4.8).

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).

Close monitoring for an effect on the QTc interval is advisable.

A pre-treatment cardiovascular examination, including a baseline ECG and an echocardiography is recommended prior to initiating therapy with anagrelide. Patients should be monitored during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation. Hypokalaemia or hypomagnesaemia must be corrected prior to anagrelide administration and should be monitored periodically during therapy.

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III and because of its positive inotropic and chronotropic effects, anagrelide should be used with caution in patients of any age with known or suspected heart disease. Moreover, serious cardiovascular adverse events have also occurred in patients without suspected heart disease and with normal pre-treatment cardiovascular examination.

Anagrelide should only be used if the potential benefits of therapy outweigh the potential risks.

Paediatric population
Limited data are available on the use of anagrelide in the paediatric population and anagrelide should be used in this patient group with caution (see sections 5.1 and 5.2).

Clinically relevant interactions
Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III (PDE III). Concomitant use of anagrelide with other PDE III inhibitors such as milrinone, amrinone, enoximone, olprinone and cilostazol is not recommended.
Agrylin contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drug interactions: effects of other substances on anagrelide

- Anagrelide is primarily metabolised by CYP1A2. It is known that CYP1A2 is inhibited by several medicinal products, including fluvoxamine and enoxacin, and such medicinal products could theoretically adversely influence the clearance of anagrelide.
- *In vivo* interaction studies in humans have demonstrated that digoxin and warfarin do not affect the pharmacokinetic properties of anagrelide.

Drug interactions: effects of anagrelide on other substances

- Anagrelide demonstrates some limited inhibitory activity towards CYP1A2 which may present a theoretical potential for interaction with other co-administered medicinal products sharing that clearance mechanism e.g. theophylline.
- Anagrelide is an inhibitor of PDE III. The effects of medicinal products with similar properties such as the inotropes milrinone, enoximone, amrinone, olprinone and cilostazol may be exacerbated by anagrelide.
- *In vivo* interaction studies in humans have demonstrated that anagrelide does not affect the pharmacokinetic properties of digoxin or warfarin.
- At the doses recommended for use in the treatment of essential thrombocythaemia, anagrelide may potentiate the effects of other medicinal products that inhibit or modify platelet function e.g. acetylsalicylic acid.
- A clinical interaction study performed in healthy subjects showed that co-administration of repeat-dose anagrelide 1 mg once daily and acetylsalicylic acid 75 mg once daily may enhance the anti-platelet aggregation effects of each drug compared with administration of acetylsalicylic acid alone. In some ET patients concomitantly treated by acetylsalicylic acid and anagrelide, major haemorrhages occurred. Therefore, the potential risks of the concomitant use of anagrelide with acetylsalicylic acid should be assessed, particularly in patients with a high risk profile for haemorrhage before treatment is initiated.
- Anagrelide may cause intestinal disturbance in some patients and compromise the absorption of hormonal oral contraceptives.

Food interactions

- Food delays the absorption of anagrelide, but does not significantly alter systemic exposure.
- The effects of food on bioavailability are not considered clinically relevant to the use of anagrelide.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
Women of child-bearing potential should use adequate birth-control measures during treatment with anagrelide.

Pregnancy
There are no adequate data from the use of anagrelide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Therefore Agrylin is not recommended during pregnancy.

If Agrylin is used during pregnancy, or if the patient becomes pregnant while using the medicinal product, she should be advised of the potential risk to the foetus.

Breast-feeding

It is unknown whether anagrelide hydrochloride/metabolites are excreted in milk. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Agrylin.

Fertility
There are no fertility data available on anagrelide

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

In clinical development, dizziness was commonly reported. Patients are advised not to drive or operate machinery while taking Agrylin if dizziness is experienced.

4.8 Undesirable effects

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

In the later study 3660 patients who received anagrelide at a mean dose of approximately 2 mg/day were assessed for safety. In this study 34 patients received anagrelide for up to 5 years.

The most commonly reported drug related adverse reactions were headache occurring at approximately 14%, palpitations occurring at approximately 9%, fluid retention and nausea both occurring at approximately 6%, and diarrhoea occurring at 5%. These adverse drug reactions are expected based on the pharmacology of anagrelide (inhibition of PDE III). Gradual dose titration may help diminish these effects (see section 4.2).

Tabulated summary of adverse reactions
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).

MedDRA System Organ Class	Frequency of Adverse Reactions				
	Very common	*Common*	*Uncommon*	*Rare*	*Not known*
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia Pancytopenia Ecchymosis Haemorrhage		
Metabolism and nutrition disorders		Fluid retention	Oedema Weight loss	Weight gain	
Nervous system disorders	Headache	Dizziness	Paraesthesia Insomnia Depression Confusion Hypoaesthesia Nervousness Dry mouth	Somnolence Abnormal coordination Dysarthria Migraine	

MedDRA System Organ Class	Frequency of Adverse Reactions				
	Very common	*Common*	*Uncommon*	*Rare*	*Not known*
			Amnesia		
Eye disorders				Vision abnormal Diplopia	
Ear and labyrinth disorders				Tinnitus	
Cardiac disorders		Palpitations Tachycardia	Congestive heart failure Hypertension Arrhythmia Atrial fibrillation Supraventricular tachycardia Ventricular tachycardia Syncope	Angina pectoris Myocardial infarction Cardiomegaly Cardiomyopathy Pericardial effusion Vasodilatation Postural hypotension	Torsade de pointes
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis Pleural effusion Pneumonia	Pulmonary hypertension Pulmonary infiltrates	Allergic alveolitis, including interstitial lung disease and pneumonitis
Gastrointestinal disorders		Nausea Diarrhoea Abdominal pain Flatulence Vomiting	Dyspepsia Anorexia Pancreatitis Constipation Gastrointestinal haemorrhage Gastrointestinal disorder	Colitis Gastritis Gingival bleeding	
Hepatobiliary disorders			Hepatic enzymes increased		Hepatitis
Skin and subcutaneous tissue disorders		Rash	Alopecia Skin discoloration Pruritus	Dry skin	
Musculoskeletal and connective tissue disorders			Myalgia Arthralgia Back pain		
Renal and urinary disorders			Impotence	Nocturia Renal failure	Tubulointerstitial nephritis
General disorders and administration site conditions		Fatigue	Chest pain Weakness Chills Malaise Fever	Asthenia Pain Flu-like syndrome	
Investigations				Blood creatinine increased	

4.9 Overdose

Post-marketing case reports of intentional overdose with anagrelide have been received. Reported symptoms include sinus tachycardia and vomiting. Symptoms resolved with conservative management.

Agrylin, at higher than recommended doses, has been shown to produce reductions in blood pressure with occasional instances of hypotension. A single 5 mg dose of anagrelide can lead to a fall in blood pressure usually accompanied by dizziness.

A specific antidote for anagrelide has not been identified. In case of overdose, close clinical supervision of the patient is required; this includes monitoring of the platelet count for thrombocytopenia. Dose should be decreased or stopped, as appropriate, until the platelet count returns to within the normal range.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC Code: L01XX35.

The specific mechanism of action by which anagrelide reduces platelet count is not yet fully understood although it has been confirmed that anagrelide is platelet selective from *in vitro* and *in vivo* study information.

In vitro studies of human megakaryocytopoiesis established that anagrelide's inhibitory actions on platelet formation in man are mediated via retardation of maturation of megakaryocytes, and reducing their size and ploidy. Evidence of similar *in vivo* actions was observed in bone marrow biopsy samples from treated patients.

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III.

Clinical efficacy and safety
The safety and efficacy of anagrelide as a platelet lowering agent have been evaluated in four open-label, non-controlled clinical trials (study numbers 700-012, 700-014, 700-999 and 13970-301) including more than 4000 patients with myeloproliferative disorders (MPDs). In patients with essential thrombocythaemia complete response was defined as a decrease in platelet count to $\leq 600 \times 10^9$/l or a $\geq 50\%$ reduction from baseline and maintenance of the reduction for at least 4 weeks. In studies 700-012, 700-014, 700-999 and study 13970-301 the time to complete response ranged from 4 to 12 weeks. Clinical benefit in terms of thrombohaemorrhagic events has not been convincingly demonstrated.

*Effects on Heart Rate and QT*c *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 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.

A 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.

Paediatric population
An open label clinical study with a 3 month treatment period did not raise any safety concerns for anagrelide in 17 children/adolescent patients with ET (age range 7 - 14 years) compared to 18 adult patients. Earlier during clinical development a limited number (12) of children (age range 5 - 17 years) with essential thrombocythaemia were treated with anagrelide.

This medicinal product has been authorised under "Exceptional Circumstances".
This means that due to the rarity of this disease it has not been possible to obtain complete information on this medicine.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Following oral administration of anagrelide in man, at least 70% is absorbed from the gastrointestinal tract. In fasted subjects, peak plasma levels occur about 1 hour after a 0.5 mg dose; the plasma half-life is short, approximately 1.3 hours. Dose proportionality has been found in the dose range 0.5 mg to 2 mg.

Anagrelide is primarily metabolised by CYP1A2; less than 1% is recovered in the urine as anagrelide. Two major urinary metabolites, 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline and 3-hydroxy anagrelide have been identified. The mean recovery of 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline in urine is approximately 18-35% of the administered dose.

Pharmacokinetic data from healthy subjects established that food decreases the C_{max} of anagrelide by 14%, but increases the AUC by 20%. Food had a more significant effect on the active metabolite and decreased the C_{max} by 29%, although it had no effect on the AUC.

As expected from its half-life, there is no evidence for anagrelide accumulation in the plasma. Additionally these results show no evidence of auto-induction of the anagrelide clearance.

Paediatric population
Pharmacokinetic data from fasting children and adolescents (age range 7 - 14 years) with essential thrombocythaemia indicate that dose and body weight normalised exposure, C_{max} and AUC, of anagrelide were lower in children/adolescents compared to adults. There was also a trend to lower exposure to the active metabolite. These observations may be a reflection of more efficient metabolic clearance in younger subjects.

Older people
Pharmacokinetic data from fasting older 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 older patients, but that the C_{max} and AUC of the active metabolite, 3-hydroxy anagrelide, were 42% and 37% lower respectively in the older patients. These differences were likely to be caused by lower presystemic metabolism of anagrelide to 3-hydroxy anagrelide in the older patients.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Repeated dose toxicity
Following repeated administration of anagrelide, at doses of 1 mg/kg/day or higher, subendocardial haemorrhage and focal myocardial necrosis occurred in dogs.

Reproductive toxicology
Maternally toxic doses of anagrelide (60 mg/kg/day and above) in rats and rabbits were associated with increased embryo resorption and foetal mortality.

Mutagenic and carcinogenic potential
Studies on the genotoxic potential of anagrelide did not identify any mutagenic or clastogenic effects.

In a two-year rat carcinogenicity study, non-neoplastic and neoplastic findings were observed and related or attributed to an exaggerated pharmacological effect. Among them, the incidence of adrenal phaeochromocytomas was increased relative to control in males at all dose levels (≥ 3 mg/kg/day) and in females receiving 10 mg/kg/day and above. The lowest dose in males (3 mg/kg/day) corresponds to 37 times the human AUC exposure after a 1 mg twice daily dose. Uterine adenocarcinomas, of epigenetic origin, could be related to an enzyme induction of CYP1 family. They were observed in females receiving 30 mg/kg/day, corresponding to 572 times the human AUC exposure after a 1 mg twice daily dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Povidone (E1201)
Anhydrous lactose
Lactose monohydrate
Microcrystalline cellulose (E460)
Crospovidone
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac
Strong ammonium solution
Potassium hydroxide (E525)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage
Store below 25ºC

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with child-resistant closures and desiccant containing 100 capsules.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

Shire Pharmaceutical Contracts
Hampshire International Business Park
Chineham
Basingstoke
Hampshire RG24 8EP
United Kingdom

8. License Holder

Medison Pharma Ltd. , POB 7090, PetachTikva