Agrylin® capsules 0.5 mg
Anagrelide (as hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

Agrylin capsules 0.5mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5mg anagrelide (equivalent to 0.61mg anagrelide hydrochloride).

For a 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

Agrylin capsules are indicated for the treatment of patients with essential thrombocythaemia (ET) to reduce the elevated platelet counts.

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 dosage of anagrelide is 1mg/day, which should be administered orally, in two divided doses (0.5mg/dose).

The starting dose should be maintained for at least one week. After one week the dosage may be titrated, on an individual basis, to achieve the lowest effective dosage 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 dosage increment must not exceed 0.5mg/day in any one week and the maximum single dose should not exceed 2.5mg (see section 4.9). During clinical development dosages of 10mg/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 >1mg/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 dosage of 1 to 3mg/day (for further information on the clinical effects refer to 5.1).

Elderly: The observed pharmacokinetic differences between elderly 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 the clinical development approximately 50% of the patients treated with anagrelide were over 60 years of age and no age specific alterations in dosage 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: Currently, there are no specific pharmacokinetic data for this patient population and 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: Currently, there are no specific 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 patients: The experience in children is limited; anagrelide should be used in this patient group with caution (see sections 5.1 and 5.2).

4.3 Contraindications

Hypersensitivity to anagrelide or any of the excipients of the medicinal product.

Patients with moderate or severe hepatic impairment.

Patients with moderate or severe renal impairment (creatinine clearance <50mL/min).

4.4 Special warnings and special precautions for use

Hepatic impairment: (See sections 4.2 and 4.3) 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).

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

Monitoring: Therapy requires close clinical supervision of the patient which will include a full blood count (haemoglobin and white blood cell and platelet counts), renal function (serum creatinine and urea) tests and electrolytes (potassium, magnesium and calcium). As cases of hepatitis have been reported from postmarketing surveillance, it is recommended that liver function tests (ALT and AST) are performed before anagrelide treatment is initiated and at regular intervals thereafter.

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. Patients should be advised how to recognize 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, the rebound in platelet count is variable, but the platelet count will start to increase within 4 days of stopping treatment with Agrylin capsules and will return to pre-treatment levels within 10 to 14 days. possibly rebounding above baseline values. Therefore platelets should be monitored frequently.

Cardiovascular: Cases of cardiomegaly and congestive heart failure have been reported (see section 4.8). Anagrelide should be used with caution in patients of any age with known or suspected heart disease, and only if the potential benefits of therapy outweigh the potential risks. Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III and because of its positive inotropic and chronotropic effects, a pre-treatment cardiovascular examination (including further investigation such as echocardiography, electrocardiogram) is recommended for all patients. Patients should be monitored during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation.

Anagrelide has been shown to increase the heart rate, resulting in an apparent increase in QTc interval of the electrocardiogram in healthy volunteers. The clinical impact of this effect is unknown (see section 5.1).

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).

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.

Paediatric patients: (See sections 4.2 and 5.2) Limited data are available on the use of anagrelide in the paediatric population and anagrelide should be used in this patient group with caution.

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. The 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, before treatment is commenced.

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

4.5 Interaction with other medicinal products and other forms of interaction

Limited pharmacokinetic and/or pharmacodynamlc studies investigating possible interactions between anagrelide and other drugs have been conducted.

Drug interactions: effects of other substances on anagrelide

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

CYP1A2 inhibitors

- Anagrelide is primarily metabolised by CYP1A2. It is known that CYP1A2 is inhibited by several medicinal products, including fluvoxamine and omeprazole, and such medicinal products could theoretically adversely influence the clearance of anagrelide.

CYP1A2 inducers

- CYP1A2 inducers (such as omeprazole) could decrease the exposure of anagrelide (see section 5.2). The consequences on the safety and efficacy profile of anagrelide are not established. Therefore, clinical and biological monitoring is recommended in patients taking concomitant CYP1A2 inducers. If needed, anagrelide dose adjustment could be made.

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.
- In two clinical interaction studies in healthy subjects, co-administration of single-dose anagrelide 1mg and acetylsalicylic acid 900mg or repeat-dose anagrelide 1mg once daily and acetylsalicylic acid 75mg once daily showed greater anti-platelet aggregation effects than administration of acetylsalicylic acid alone. In the repeat-dose study, there was a short-lived decrease in *ex vivo* collagen-induced platelet aggregation beyond the effects of acetylsalicylic acid alone for the first 2 hours after administration.

  Co-administered anagrelide 1mg and acetylsalicylic acid 900mg single-doses had no effect on bleeding time, prothrombin time (PT) or activated partial thromboplastin time (aPTT). In some ET patients concomitantly treated by anagrelide and acetylsalicylic acid, major haemorrhages occurred. Therefore, the potential risks and benefits of concomitant use of anagrelide with acetylsalicylic acid should be assessed, particularly in patients with a high risk profile for haemorrhage, before treatment is commenced.
- 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.

4.6 Pregnancy and lactation

Pregnancy: Data on a limited number (14) of exposed pregnancies indicate no adequate evidence supporting safe use of anagrelide on pregnancy or health of the fetus or development of the child if anagrelide is inadvertently taken during the first three months of pregnancy. Three (3/14) patients had a pregnancy of unknown outcome. Four (4/14) patients underwent termination of the pregnancy due to medical complications not associated with anagrelide. One (1/14) patient had a spontaneous abortion. The information is from clinical trial and pharmacovigilance reporting. To date, no other relevant epidemiological data are available.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Use of Agrylin during pregnancy is not recommended. If Agrylin is used during pregnancy, or if the patient becomes pregnant while using the drug, she should be advised of the potential risk to the fetus.

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

Lactation: It is not known whether anagrelide hydrochloride is excreted in milk. Since many drugs are excreted in human milk and because of the potential for adverse reactions in breast-feeding infants, mothers should discontinue breast-feeding when taking Agrylin.

4.7 Effects on ability to drive and use machines

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

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 2mg/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 2mg/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).

The following convention was used for frequency of adverse drug reactions: 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); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Common: Anaemia
Uncommon: Thrombocytopenia, pancytopenia, ecchymosis, haemorrhage

Metabolism and nutrition disorders
Common: Fluid retention
Uncommon: Oedema, weight loss
Rare: Weight gain

Nervous system disorders
Very common: Headache
Common: Dizziness
Uncommon: Paraesthesia, insomnia, depression, confusion, hypoaesthesia, nervousness, dry mouth, amnesia
Rare: Somnolence, abnormal coordination, dysarthria, migraine
Not known: Cerebral infarction

Eye disorders
Rare: Vision abnormal, diplopia

Ear and labyrinth disorders
Rare: Tinnitus

Cardiac disorders
Common: Palpitations, tachycardia
Uncommon: Congestive heart failure, hypertension, arrhythmia, atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, syncope,
Rare: Angina pectoris, myocardial infarction, cardiomegaly, cardiomyopathy, pericardial effusion, vasodilatation, postural hypotension, Prinzmetal angina
Not known Torsades de pointes

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, epistaxis, pleural effusion, pneumonia, Pulmonary hypertension
Rare: Pulmonary infiltrates
Not known: Allergic alveolitis, including lung disease and pneumonitis

Gastrointestinal disorders
Common: Nausea, diarrhoea, abdominal pain, flatulence, vomiting
Uncommon: Dyspepsia, anorexia, pancreatitis, constipation, gastrointestinal haemorrhage, gastrointestinal disorder
Rare: Colitis, gastritis, gingival bleeding

Hepatobiliary disorders
Uncommon: Hepatic enzymes increased
Not known: Hepatitis

Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Alopecia, skin discoloration, pruritus
Rare: Dry skin

Musculoskeletal and connective tissue disorders
Uncommon: Myalgia, arthralgia, back pain

Renal and urinary disorders
Uncommon: Impotence
Rare: Nocturia, renal failure
Not known: Tubulointerstitial nephritis

Investigations
Rare: Blood creatinine increased

General disorders and administration site conditions
Common: Fatigue
Uncommon: Chest pain, weakness, chills, malaise, fever
Rare: Asthenia, pain, flu-like syndrome

4.9 Overdose

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.

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. Dosage should be decreased or stopped, as appropriate, until the platelet count returns to within the normal range.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
ATC Code: L01XX35 (Other Antineoplastic Agents)

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.

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.

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 neoplasms (MPNs). 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.

Paediatric patients: 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.

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 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 repolarisation.

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 0.5mg dose; the plasma half-life is short, approximately 1.3 hours. Dose proportionality has been found in the dose range 0.5mg to 2mg.

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.

The effect of omeprazole, a CYP1A2 inducer, on the pharmacokinetics of anagrelide was investigated in 20 healthy adult subjects following multiple, once daily 40-mg doses. The results showed that in the presence of omeprazole, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} of anagrelide were reduced by 27%, 26%, and 36%, respectively; and the corresponding values for 3-hydroxy anagrelide, a metabolite of anagrelide, were reduced by 13%, 14%, and 18%, respectively.

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.

Special Populations

Paediatric patients: 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.

Elderly: 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.

5.3 Preclinical safety data

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

Reproductive toxicity: Maternally toxic dosages of anagrelide (60mg/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
($\geq$3mg/kg/day) and in females receiving 10 mg/kg/day and above. The lowest dose in males (3mg/kg/day) corresponds to 37 times the human AUC exposure after a 1mg twice daily dose. Uterine adenocarcinomas, of epigenetic origin, could be related to an enzyme induction of CYP1 family. They were observed in females receiving 30mg/kg/day, corresponding to 572 times the human AUC exposure after a 1mg twice daily dose.

Currently there is no clinical evidence that these findings are of relevance to human use.

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
Dehydrated alcohol
Isopropyl alcohol
Butyl alcohol
Propylene glycol
Strong ammonium solution

Potassium hydroxide (E525)
Black iron oxide (E172)
Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

HDPE bottles containing desiccant with child-resistant closures containing 100 capsules.

6.6 Instructions for use and handling

No special requirements.

7. MANUFACTURER/REPACKER

Manufactured by: Patheon Manufacturing Services, LLC.
5900 Martin Luther King Jr. Highway,
Greenville, NC 27834, USA

8. DATE OF TEXT

May 2022