ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Anagrelide Viatris 0.5 mg hard capsules
Anagrelide Viatris 1 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Anagrelide Viatris 0.5 mg hard capsules

Each hard capsule contains anagrelide hydrochloride monohydrate equivalent to 0.5 mg anagrelide.

Excipients with known effect

Each hard capsule contains approximately 59.5 mg lactose.

Anagrelide Viatris 1 mg hard capsules

Each hard capsule contains anagrelide hydrochloride monohydrate equivalent to 1 mg anagrelide.

Excipients with known effect

Each hard capsule contains approximately 119 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Anagrelide Viatris 0.5 mg hard capsules
A capsule size 4 (approximately 14.3 x 5.3 mm) with an opaque white body and cap. The capsule is filled with white to off-white powder.

Anagrelide Viatris 1 mg hard capsules
A capsule size 4 (approximately 14.3 x 5.3 mm) with a grey body and cap. The capsule is filled with white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anagrelide is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

An at-risk patient
An at-risk ET patient is defined by one or more of the following features:

- > 60 years of age or
- a platelet count >1,000 x 10^9/l or
- a history of thrombo-haemorrhagic events.

4.2 Posology and method of administration

Treatment with anagrelide should be initiated by a clinician with experience in the management of ET.

Posology

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).

Special populations

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 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 reactions (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 (see section 4.3).

Hepatic impairment
There are limited pharmacokinetic data for this patient population. However, hepatic metabolism represents the major route of anagrelide 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 safety and efficacy of anagrelide in children have not been established. The experience in children and adolescents is very limited; anagrelide should be used in this patient group with caution. In the absence of specific paediatric guidelines, WHO diagnostic criteria for adult diagnosis of ET are considered to be of relevance to the paediatric population. Diagnostic guidelines for ET should be followed carefully and diagnosis reassessed periodically in cases of uncertainty, with effort made to distinguish from hereditary or secondary thrombocytosis, which may include genetic analysis and bone marrow biopsy.

Typically, cytoreductive therapy is considered in high-risk paediatric patients.

Anagrelide treatment should only be initiated when the patient shows signs of disease progression or suffers from thrombosis. If treatment is initiated, the benefits and risks of treatment with anagrelide must be monitored regularly and the need for ongoing treatment evaluated periodically.

Platelet targets are assigned on an individual patient basis by the treating physician.

Discontinuation of treatment should be considered in paediatric patients who do not have a satisfactory treatment response after approximately 3 months (see section 4.4).

Currently available data are described in sections 4.4, 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Anagrelide Viatris is for oral use. The capsules must be swallowed whole. The contents of the capsules should not be crushed or diluted in a liquid.

4.3 Contraindications

Hypersensitivity to the active substance 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).

Thrombotic risk

Abrupt treatment discontinuation 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 anagrelide and will return to pre-treatment levels within 10 to 14 days, possibly rebounding above baseline values. Therefore, platelets should be monitored frequently (see section 4.2).

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).

Cardiovascular

Serious cardiovascular adverse reactions 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 echocardiography is recommended for all patients prior to initiating therapy with anagrelide. All patients should be monitored regularly during treatment (e.g., ECG or echocardiography) 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 reactions 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.

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 population

Very 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 4.2, 4.8, 5.1 and 5.2).

As with the adult population, a full blood count and assessment of cardiac, hepatic and renal function should be undertaken before treatment and regularly during treatment. The disease may progress to myelofibrosis or AML. Although the rate of such progression is not known, children have a longer disease course and may, therefore, be at increased risk for malignant transformation, relative to adults. Children should be monitored regularly for disease progression according to standard clinical practices, such as physical examination, assessment of relevant disease markers and bone marrow biopsy.

Any abnormalities should be evaluated promptly and appropriate measures taken, which may also include dose reduction, interruption or discontinuation.

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.

Use of concomitant anagrelide and acetylsalicylic acid has been associated with major haemorrhagic events (see section 4.5).

Excipients

Anagrelide Viatris contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Anagrelide Viatris contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

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.

Effects of other active 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 enoxacin, 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.

Effects of anagrelide on other active 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 ET, 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 active substance compared with administration of acetylsalicylic acid alone. In some patients with ET 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, anagrelide is not recommended during pregnancy.

If anagrelide 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/metabolites are excreted in human milk. Available data in animals have shown excretion of anagrelide/metabolites in milk. A risk to the breast-fed newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with anagrelide.

Fertility

No human data on the effect of anagrelide on fertility are available. In male rats, there was no effect on fertility or reproductive performance with anagrelide. In female rats, using doses in excess of the therapeutic range, anagrelide disrupted implantation (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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 3,660 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 adverse reactions associated with anagrelide 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 list 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	**Frequency of adverse reactions**				
	Very common	***Common***	***Uncommon***	***Rare***	***Not known***
Blood and lymphatic system disorders		Anaemia	Pancytopenia Thrombocytopenia Haemorrhage Ecchymosis		
Metabolism and nutrition disorders		Fluid retention	Oedema Weight loss	Weight gain	
Nervous system disorders	Headache	Dizziness	Depression Amnesia Confusion Insomnia Paraesthesia Hypoaesthesia Nervousness Dry mouth	Migraine Dysarthria Somnolence Abnormal coordination	Cerebral infarction*
Eye disorders				Diplopia Vision abnormal	
Ear and labyrinth disorders				Tinnitus	
Cardiac disorders		Tachycardia Palpitations	Ventricular tachycardia Congestive heart failure Atrial fibrillation Supraventricular tachycardia Arrhythmia Hypertension Syncope	Myocardial infarction Cardiomyopathy Cardiomegaly Pericardial effusion Angina pectoris Postural hypotension Vasodilation Prinzmetal angina	Torsade de pointes
Respiratory, thoracic and mediastinal disorders			Pulmonary hypertension Pneumonia Pleural effusion	Pulmonary infiltrates	Interstitial lung disease including pneumonitis and allergic alveolitis

MedDRA System Organ Class	Frequency of adverse reactions				
	Very common	***Common***	***Uncommon***	***Rare***	***Not known***
			Dyspnoea Epistaxis		
Gastrointestinal disorders		Diarrhoea Vomiting Abdominal pain Nausea Flatulence	Gastrointestinal haemorrhage Pancreatitis Anorexia Dyspepsia Constipation Gastrointestinal disorder	Colitis Gastritis Gingival bleeding	
Hepatobiliary disorders			Hepatic enzymes increased		Hepatitis
Skin and subcutaneous tissue disorders		Rash	Alopecia Pruritus Skin discolouration	Dry skin	
Musculoskeletal and connective tissue disorders			Arthralgia Myalgia Back pain		
Renal and urinary disorders			Impotence	Renal failure Nocturia	Tubulointerstitial nephritis
General disorders and administration site conditions		Fatigue	Chest pain Fever Chills Malaise Weakness	Flu-like syndrome Pain Asthenia	
Investigations				Blood creatinine increased	

* Cerebral infarction (see section 4.4 Thrombotic Risk)

Paediatric population

48 patients aged 6 through17 years (19 children and 29 adolescents) have received anagrelide for up to 6.5 years either in clinical studies or as part of a disease registry (see section 5.1).
The majority of adverse reactions observed were among those listed in the SmPC. However, safety data are limited and do not allow a meaningful comparison between adult and paediatric patients to be made (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

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.

Anagrelide, 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 (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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.

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 studies (study numbers 700-012, 700-014, 700-999 and 13970-301) including more than 4,000 patients with myeloproliferative neoplasms (MPNs). In patients with ET 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 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.

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

In an open-label clinical study in 8 children and 10 adolescents (including patients who were anagrelide treatment naïve or who had been receiving anagrelide for up to 5 years pre-study), median platelet counts were decreased to controlled levels after 12 weeks of treatment. The average daily dose tended to be higher in adolescents.

In a paediatric registry study, median platelet counts were reduced from diagnosis and maintained for up to 18 months in 14 paediatric patients with ET (4 children, 10 adolescents) with anagrelide treatment. In earlier, open-label studies, median platelet count reductions were observed in 7 children and 9 adolescents treated for between 3 months and 6.5 years.

The average total daily dose of anagrelide across all studies in paediatric patients with ET was highly variable, but overall the data suggest that adolescents could follow similar starting and maintenance doses to adults and that a lower starting dose of 0.5 mg/day would be more appropriate for children over 6 years (see sections 4.2, 4.4, 4.8, 5.2). In all paediatric patients, careful titration to a patient-specific daily dose is needed.

5.2 Pharmacokinetic properties

Absorption

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 administration. Pharmacokinetic data from healthy subjects established that food decreases the C_{max} of anagrelide by 14%, but increases the AUC by 20%. Food also decreased the C_{max} of the active metabolite, 3-hydroxy anagrelide, by 29%, although it had no effect on the AUC.

Biotransformation

Anagrelide is primarily metabolised by CYP1A2 to form, 3-hydroxy anagrelide, which is further metabolised via CYP1A2 to the inactive metabolite, 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline.

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.

Elimination

The plasma half-life of anagrelide is short, approximately 1.3 hours and as expected from its half-life, there is no evidence for anagrelide accumulation in the plasma. Less than 1% is recovered in the urine as anagrelide. The mean recovery of 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline in urine is approximately 18-35% of the administered dose.

Additionally these results show no evidence of auto-induction of the anagrelide clearance.

Linearity

Dose proportionality has been found in the dose range 0.5 mg to 2 mg.

Paediatric population

Pharmacokinetic data from exposed fasting children and adolescents (age range 7 through 16 years) with ET indicate that dose normalised exposure, C_{max} and AUC, of anagrelide tended to be higher in children/adolescents compared with adults. There was also a trend to higher dose-normalised exposure to the active metabolite.

Elderly

Pharmacokinetic data from fasting elderly patients with ET (age range 65 through 75 years) compared to fasting adult patients (age range 22 through 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 oral administration of anagrelide in dogs, subendocardial haemorrhage and focal myocardial necrosis was observed at 1 mg/kg/day or higher in males and females with males being more sensitive. The no observed effect level (NOEL) for male dogs (0.3 mg/kg/day) corresponds to 0.1-, 0.1-, and 1.6-fold the AUC in humans for anagrelide at 2 mg/day, and the metabolites BCH24426 and RL603, respectively.

Reproductive toxicology

Fertility
In male rats, anagrelide at oral doses up to 240 mg/kg/day (>1,000 times a 2-mg/day dose, based on body surface area) was found to have no effect on fertility and reproductive performance. In female rats increases in pre- and post-implantation losses and a decrease in the mean number of live embryos was observed at 30 mg/kg/day. The NOEL (10 mg/kg/day) to this effect was 143-, 12- and 11-fold higher than the AUC in humans administered a dose of anagrelide 2 mg/day, and the metabolites BCH24426 and RL603, respectively.

Embryofoetal development studies
Maternally toxic doses of anagrelide in rats and rabbits were associated with increased embryo resorption and foetal mortality.

In a pre- and post-natal development study in female rats, anagrelide at oral doses of ≥10 mg/kg produced a non-adverse increase in gestational duration. At the NOEL dose (3 mg/kg/day), the AUCs for anagrelide and the metabolites BCH24426 and RL603 were 14-, 2- and 2-fold higher than the AUC in humans administered an oral dose of anagrelide 2 mg/day.

Anagrelide at ≥ 60 mg/kg increased parturition time and mortality in the dam and foetus, respectively. At the NOEL dose (30 mg/kg/day), the AUCs for anagrelide and the metabolites BCH24426 and RL603 were 425-, 31- and 13-fold higher than the AUC in humans administered an oral dose of anagrelide 2 mg/day, respectively.

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

Lactose
Lactose monohydrate
Croscarmellose sodium
Povidone (K29/32)
Microcrystalline cellulose
Magnesium stearate

Capsule shell

Anagrelide Viatris 0.5 mg hard capsules
Gelatin
Titanium dioxide (E171)

Anagrelide Viatris 1 mg hard capsules
Gelatin
Titanium dioxide (E171)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Anagrelide 0.5 mg hard capsules
Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

Anagrelide 1 mg hard capsules
Store in the original package in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle of 30 ml or 75 ml with a tamper evident, child-resistant polypropylene (PP) closure with a desiccant.

Pack size: 100 hard capsules.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park
Mulhuddart, Dublin 15
DUBLIN
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/17/1256/001
EU/1/17/1256/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2018
Date of latest renewal: 21 November 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

SYNTHON HISPANIA, S.L.
C/ Castello, nº1, Pol. Las Salinas
Sant Boi de Llobregat
Barcelona, 08830
Spain

Synthon BV
Microweg 22
6545 CM Nijmegen
NETHERLANDS

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Anagrelide Viatris 0.5 mg hard capsules
anagrelide

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains anagrelide hydrochloride monohydrate equivalent to 0.5 mg anagrelide.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

100 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORE OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park
Mulhuddart, Dublin 15
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1256/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Carton only:
anagrelide Viatris 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Carton only:
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Carton only:
PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Anagrelide Viatris 1 mg hard capsules
anagrelide

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains anagrelide hydrochloride monohydrate equivalent to 1 mg anagrelide.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

100 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORE OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park
Mulhuddart, Dublin 15
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1256/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Carton only:
anagrelide Viatris 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Carton only:
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Carton only:
PC
SN
NN

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Anagrelide Viatris 0.5 mg hard capsules

anagrelide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Anagrelide Viatris is and what it is used for

Anagrelide Viatris contains the active substance, anagrelide. Anagrelide is a medicine which interferes with the development of platelets. It reduces the number of platelets produced by the bone marrow, which results in a decrease in the platelet count in the blood towards a more normal level. For this reason, it is used to treat patients with essential thrombocythaemia.

Essential thrombocythaemia is a condition which occurs when the bone marrow produces too many of the blood cells known as platelets. Large numbers of platelets in the blood can cause serious problems with blood circulation and clotting.

2. What you need to know before you take Anagrelide Viatris

Do not take Anagrelide Viatris
- If you are allergic to anagrelide or any of the other ingredients of this medicine (listed in section 6). An allergic reaction may be recognised as a rash, itching, swollen face or lips, or shortness of breath;
- If you have moderate or severe liver problems;
- If you have moderate or severe kidney problems.

Warnings and precautions
Talk to your doctor before taking Anagrelide Viatris:
- If you have or think you might have a problem with your heart;
- If you were born with or have family history of prolonged QT interval (seen on ECG, electrical recording of the heart), or you are taking other medicines that result in abnormal ECG changes or if you have low levels of electrolytes, e.g., potassium, magnesium or calcium (see section "Other medicines and Anagrelide Viatris");
- If you have any problems with your liver or kidneys.

In combination with acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting, also known as aspirin), there is an increased risk

of major haemorrhages (bleeding) (see section "Other medicines and Anagrelide Viatris").

While taking Anagrelide Viatris, you should take the exact dose prescribed by your doctor. Do not stop taking the medicine without first talking to your doctor. Do not abruptly stop taking this medicine without consulting your doctor. Abrupt withdrawal of medicine may lead to increased risk of stroke.

Signs and symptoms of stroke may include sudden numbness or weakness in the face, arm, or leg, especially on one side of the body, sudden confusion, trouble speaking, or difficulty understanding speech, sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance, or lack of coordination and sudden severe headache with no known cause. Please seek immediate medical help.

Children and adolescents
There is limited information on the use of anagrelide in children and adolescents and therefore this medicine should be used with caution.

Other medicines and Anagrelide Viatris
Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Tell your doctor if you are taking any of the following medicines:
- Medicines that can alter your heart rhythm, e.g., sotalol, amiodarone;
- Fluvoxamine, used to treat depression;
- Certain types of antibiotic, such as enoxacin, used to treat infections;
- Theophylline, used to treat severe asthma and breathing problems;
- Medicines used to treat heart disorders, for example, milrinone, enoximone, amrinone, olprinone and cilostazol;
- Acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting, also known as aspirin);
- Other medicines used to treat conditions affecting the platelets in your blood, e.g., clopidogrel;
- Omeprazole, used to reduce the amount of acid produced in the stomach;
- Oral contraceptives: If you experience bad diarrhoea whilst taking this medicine, it may reduce how well the oral contraceptive works and use of an extra method of contraception is recommended (e.g., condom). See the instructions in the patient leaflet of the contraceptive pill you are taking.

Anagrelide or these medicines may not work properly if taken together.

If you are not sure, speak to your doctor or pharmacist for advice.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or are planning to become pregnant. Anagrelide Viatris should not be taken by pregnant women. Women who are at risk of becoming pregnant should make sure that they are using effective contraception when taking anagrelide. Speak to your doctor if you need advice with contraception.

Tell your doctor if you are breast-feeding or if you are planning to breast-feed your baby. Anagrelide Viatris should not be taken while breast-feeding. You must stop breast-feeding if you are taking Anagrelide Viatris.

Driving and using machines
Dizziness has been reported by some patients taking anagrelide. Do not drive or use machines if you feel dizzy.

Anagrelide Viatris contains lactose and sodium

This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

3. How to take Anagrelide Viatris

Always take Anagrelide Viatris exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The amount of anagrelide that people take can be different, and this depends on your condition. Your doctor will prescribe the best dose for you.

The usual starting dose of this medicine is 1 mg. You take this dose as one capsule of 0.5 mg twice a day, for at least a week. After this time, your doctor may either increase or decrease the number of capsules that you take to find the dose best suited to you and which treats your condition most effectively.

Your capsules should be swallowed whole with a glass of water. Do not crush the capsules or dilute the contents in a liquid. You can take the capsules with food or after a meal or on an empty stomach. It is best to take the capsule(s) at the same time every day.

Do not take more or less capsules than your doctor has recommended. **Do not** stop taking the medicine without first talking to your doctor. You should not suddenly stop taking this medicine on your own.

Your doctor will ask you to have blood tests at regular intervals to check that your medicine is working effectively and that your liver and kidneys are working well.

If you take more Anagrelide Viatris than you should
If you take more Anagrelide Viatris than you should or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the pack of Anagrelide Viatris.

If you forget to take Anagrelide Viatris
Take your capsules as soon as you remember. Take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you are worried, speak to your doctor.

Serious side effects
Uncommon: Heart failure (signs include shortness of breath, chest pain, swelling of the legs due to fluid build-up), severe problem with the rate or rhythm of the heartbeat (ventricular tachycardia, supraventricular tachycardia or atrial fibrillation), inflammation of the pancreas which causes severe abdominal and back pain (pancreatitis), vomiting blood or passing bloody or black stools, severe reduction in blood cells which can cause weakness, bruising, bleeding or infections (pancytopenia), increased pressure in the lung arteries (signs include shortness of breath, swelling in legs or ankles and lips and skin can turn bluish colour).
Rare: Kidney failure (when you pass little or no urine), heart attack.

If you notice any of these side effects, contact your doctor <u>immediately</u>.

Other possible side effects
Very common side effects (may affect more than 1 in 10 people):
Headache.

Common side effects (may affect up to 1 in 10 people):
Dizziness, tiredness, rapid heartbeat, irregular or strong heartbeat (palpitations), feeling sick (nausea), diarrhoea, stomach pain, wind, being sick (vomiting), reduction in red blood cell count (anaemia), fluid retention or rash.

Uncommon side effects (may affect up to 1 in 100 people):
A feeling of weakness or feeling unwell, high blood pressure, irregular heartbeat, fainting, chills or fever, indigestion, loss of appetite, constipation, bruising, bleeding, swelling (oedema), weight loss, muscle aches, painful joints, back pain, decreased or loss of feeling or sensation such as numbness, especially in the skin, abnormal feeling or sensation such as tingling and 'pins and needles', sleeplessness, depression, confusion, nervousness, dry mouth, loss of memory, breathlessness, nosebleed, serious lung infection with fever, shortness of breath, cough, phlegm; hair loss, skin itching or discolouration, impotence, chest pain, reduction in blood platelets, which increases the risk of bleeding or bruising (thrombocytopenia), accumulation of fluid around the lungs or an increase in liver enzymes. Your doctor may do a blood test which may show an increase in your liver enzymes.

Rare side effects (may affect up to 1 in 1,000 people):
Bleeding gums, weight gain, severe chest pain (angina pectoris), heart muscle disease, (signs include fatigue, chest pain and palpitations), enlarged heart, accumulation of fluid around the heart, painful spasm of the blood vessels on the heart (while resting, usually at night or early morning) (Prinzmetal angina), loss of coordination, difficulty in speaking, dry skin, migraine, visual disturbances or double vision, ringing in the ears, dizziness on standing up (especially when getting up from a sitting or lying position), increased need to pass water at night, pain, 'flu-like' symptoms, sleepiness, widening of blood vessels, inflammation of the large bowel (signs include: diarrhoea, usually with blood and mucus, stomach pain, fever), inflammation of the stomach (signs include: pain, nausea, vomiting), area of abnormal density in the lung, increased creatinine level in blood tests, which may be a sign of kidney problems.

The following side effects have been reported but it is not known exactly how often they occur:
- Potentially life-threatening, irregular heartbeat (Torsade de pointes);
- Inflammation of the liver, symptoms include nausea, vomiting, itching, yellowing of the skin and eyes, discoloration of stool and urine (hepatitis);
- Lung inflammation (signs include fever, coughing, difficulty breathing, wheezing; which causes scaring of the lungs) (allergic alveolitis, including interstitial lung disease, pneumonitis);
- Inflammation of the kidneys (tubulointerstitial nephritis).
- Stroke (see section 2).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Anagrelide Viatris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.

This medicinal product does not require any special temperature storage conditions.

If your doctor stops your medicine, do not keep any leftover capsules unless your doctor tells you to. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Anagrelide Viatris contains
The active substance is anagrelide. Each capsule contains anagrelide hydrochloride monohydrate equivalent to 0.5 mg anagrelide.
The other ingredients are lactose, croscarmellose sodium, povidone, microcrystalline cellulose, magnesium stearate, gelatin and titanium dioxide(E171). See section 2 ‘Anagrelide Viatris contains lactose and sodium’.

What Anagrelide Viatris looks like and contents of the pack
Anagrelide Viatris 0.5 mg hard capsules have a white body and cap. The capsule is filled with a white to off-white powder.
The capsule size is approximately 14.3 x 5.3 mm.

Anagrelide Viatris is available in plastic bottles of 30 ml or 75 ml with a tamper evident, child-resistant closure and a desiccant. Each bottle contains 100 hard capsules.

Marketing Authorisation Holder
Viatris Limited
Damastown Industrial Park
Mulhuddart, Dublin 15
DUBLIN
Ireland

Manufacturer
Synthon Hispania SL
C/ Castelló no1
POL. Las Salinas
Sant Boi de Llobregat
08830 Barcelona
Spain

Synthon BV
Microweg 22
6545 CM Nijmegen
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Viatris
Tél/Tel: + 32 (0)2 658 61 00

България
Майлан ЕООД
Тел: +359 2 44 55 400

Lietuva
Viatris UAB
Tel: +370 5 205 1288

Luxembourg/Luxemburg
Viatris
Tél/Tel: + 32 (0)2 658 61 00
(Belgique/Belgien)

Česká republika
Viatris CZ s.r.o.
Tel: + 420 222 004 400

Danmark
Viatris ApS
Tlf: +45 28 11 69 32

Deutschland
Viatris Healthcare GmbH
Tel: +49 800 0700 800

Eesti
Viatris OÜ
Tel: + 372 6363 052

Ελλάδα
Viatris Hellas Ltd
Τηλ: +30 2100 100 002

España
Viatris Pharmaceuticals, S.L.
Tel: + 34 900 102 712

France
Viatris Santé
Tél: +33 4 37 25 75 00

Hrvatska
Viatris Hrvatska d.o.o.
Tel: +385 1 23 50 599

Ireland
Viatris Limited
Tel: +353 1 8711600

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Viatris Italia S.r.l.
Tel: + 39 (0) 2 612 46921

Κύπρος
CPO Pharmaceuticals Limited
Τηλ: +357 22863100

Latvija
Viatris SIA
Tel: +371 676 055 80

Magyarország
Viatris Healthcare Kft.
Tel.: + 36 1 465 2100

Malta
V.J. Salomone Pharma Ltd
Tel: + 356 21 22 01 74

Nederland
Mylan BV
Tel: + 31 (0)20 426 3300

Norge
Viatris AS
Tlf: + 47 66 75 33 00

Österreich
Viatris Austria GmbH
Tel: +43 1 86390

Polska
Viatris Healthcare Sp. z o.o.
Tel.: + 48 22 546 64 00

Portugal
Mylan, Lda.
Tel: + 351 214 127 200

România
BGP Products SRL
Tel: +40 372 579 000

Slovenija
Viatris d.o.o.
Tel: + 386 1 23 63 180

Slovenská republika
Viatris Slovakia s.r.o.
Tel: +421 2 32 199 100

Suomi/Finland
Viatris Oy
Puh/Tel**:** +358 20 720 9555

Sverige
Viatris AB
Tel: +46 (0)8 630 19 00

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Package leaflet: Information for the patient

Anagrelide Viatris 1 mg hard capsules

anagrelide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Anagrelide Viatris is and what it is used for

Anagrelide Viatris contains the active substance, anagrelide. Anagrelide is a medicine which interferes with the development of platelets. It reduces the number of platelets produced by the bone marrow, which results in a decrease in the platelet count in the blood towards a more normal level. For this reason, it is used to treat patients with essential thrombocythaemia.

Essential thrombocythaemia is a condition which occurs when the bone marrow produces too many of the blood cells known as platelets. Large numbers of platelets in the blood can cause serious problems with blood circulation and clotting.

2. What you need to know before you take Anagrelide Viatris

Do not take Anagrelide Viatris
- If you are allergic to anagrelide or any of the other ingredients of this medicine (listed in section 6). An allergic reaction may be recognised as a rash, itching, swollen face or lips, or shortness of breath;
- If you have moderate or severe liver problems;
- If you have moderate or severe kidney problems.

Warnings and precautions
Talk to your doctor before taking Anagrelide Viatris:
- If you have or think you might have a problem with your heart;
- If you were born with or have family history of prolonged QT interval (seen on ECG, electrical recording of the heart), or you are taking other medicines that result in abnormal ECG changes or if you have low levels of electrolytes, e.g., potassium, magnesium or calcium (see section "Other medicines and Anagrelide Viatris");
- If you have any problems with your liver or kidneys.

In combination with acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting, also known as aspirin), there is an increased risk

of major haemorrhages (bleeding) (see section "Other medicines and Anagrelide Viatris").

While taking Anagrelide Viatris, you should take the exact dose prescribed by your doctor. Do not stop taking the medicine without first talking to your doctor. Do not abruptly stop taking this medicine without consulting your doctor. Abrupt withdrawal of medicine may lead to increased risk of stroke.

Signs and symptoms of stroke may include sudden numbness or weakness in the face, arm, or leg, especially on one side of the body, sudden confusion, trouble speaking, or difficulty understanding speech, sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance, or lack of coordination and sudden severe headache with no known cause. Please seek immediate medical help.

Children and adolescents
There is limited information on the use of anagrelide in children and adolescents and therefore this medicine should be used with caution.

Other medicines and Anagrelide Viatris
Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Tell your doctor if you are taking any of the following medicines:
- Medicines that can alter your heart rhythm, e.g., sotalol, amiodarone;
- Fluvoxamine, used to treat depression;
- Certain types of antibiotic, such as enoxacin, used to treat infections;
- Theophylline, used to treat severe asthma and breathing problems;
- Medicines used to treat heart disorders, for example, milrinone, enoximone, amrinone, olprinone and cilostazol;
- Acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting, also known as aspirin);
- Other medicines used to treat conditions affecting the platelets in your blood, e.g., clopidogrel;
- Omeprazole, used to reduce the amount of acid produced in the stomach;
- Oral contraceptives: If you experience bad diarrhoea whilst taking this medicine, it may reduce how well the oral contraceptive works and use of an extra method of contraception is recommended (e.g., condom). See the instructions in the patient leaflet of the contraceptive pill you are taking.

Anagrelide or these medicines may not work properly if taken together.

If you are not sure, speak to your doctor or pharmacist for advice.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or are planning to become pregnant. Anagrelide Viatris should not be taken by pregnant women. Women who are at risk of becoming pregnant should make sure that they are using effective contraception when taking anagrelide. Speak to your doctor if you need advice with contraception.

Tell your doctor if you are breast-feeding or if you are planning to breast-feed your baby. Anagrelide Viatris should not be taken while breast-feeding. You must stop breast-feeding if you are taking Anagrelide Viatris.

Driving and using machines
Dizziness has been reported by some patients taking anagrelide. Do not drive or use machines if you feel dizzy.

Anagrelide Viatris contains lactose and sodium

This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

3. How to take Anagrelide Viatris

Always take Anagrelide Viatris exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The amount of anagrelide that people take can be different, and this depends on your condition. Your doctor will prescribe the best dose for you.

The usual starting dose of anagrelide is 1 mg. You take this dose as one capsule of 0.5 mg twice a day, for at least a week. After this time, your doctor may either increase or decrease the number of capsules that you take to find the dose best suited to you and which treats your condition most effectively.

Your capsules should be swallowed whole with a glass of water. Do not crush the capsules or dilute the contents in a liquid. You can take the capsules with food or after a meal or on an empty stomach. It is best to take the capsule(s) at the same time every day.

Do not take more or less capsules than your doctor has recommended. **Do not** stop taking the medicine without first talking to your doctor. You should not suddenly stop taking this medicine on your own.

Your doctor will ask you to have blood tests at regular intervals to check that your medicine is working effectively and that your liver and kidneys are working well.

If you take more Anagrelide Viatris than you should
If you take more Anagrelide Viatris than you should or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the pack of Anagrelide Viatris.

If you forget to take Anagrelide Viatris
Take your capsules as soon as you remember. Take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you are worried, speak to your doctor.

Serious side effects:
Uncommon: Heart failure (signs include shortness of breath, chest pain, swelling of the legs due to fluid build-up), severe problem with the rate or rhythm of the heartbeat (ventricular tachycardia, supraventricular tachycardia or atrial fibrillation), inflammation of the pancreas which causes severe abdominal and back pain (pancreatitis), vomiting blood or passing bloody or black stools, severe reduction in blood cells which can cause weakness, bruising, bleeding or infections (pancytopenia), increased pressure in the lung arteries (signs include shortness of breath, swelling in legs or ankles and lips and skin can turn bluish colour).
Rare: Kidney failure (when you pass little or no urine), heart attack.

If you notice any of these side effects, contact your doctor <u>immediately</u>.

Other possible side effects
Very common side effects (may affect more than 1 in 10 people):
Headache.

Common side effects (may affect up to 1 in 10 people):
Dizziness, tiredness, rapid heartbeat, irregular or strong heartbeat (palpitations), feeling sick (nausea), diarrhoea, stomach pain, wind, being sick (vomiting), reduction in red blood cell count (anaemia), fluid retention or rash.

Uncommon side effects (may affect up to 1 in 100 people):
A feeling of weakness or feeling unwell, high blood pressure, irregular heartbeat, fainting, chills or fever, indigestion, loss of appetite, constipation, bruising, bleeding, swelling (oedema), weight loss, muscle aches, painful joints, back pain, decreased or loss of feeling or sensation such as numbness, especially in the skin, abnormal feeling or sensation such as tingling and 'pins and needles', sleeplessness, depression, confusion, nervousness, dry mouth, loss of memory, breathlessness, nosebleed, serious lung infection with fever, shortness of breath, cough, phlegm; hair loss, skin itching or discolouration, impotence, chest pain, reduction in blood platelets, which increases the risk of bleeding or bruising (thrombocytopenia), accumulation of fluid around the lungs or an increase in liver enzymes. Your doctor may do a blood test which may show an increase in your liver enzymes.

Rare side effects (may affect up to 1 in 1,000 people):
Bleeding gums, weight gain, severe chest pain (angina pectoris), heart muscle disease, (signs include fatigue, chest pain and palpitations), enlarged heart, accumulation of fluid around the heart, painful spasm of the blood vessels on the heart (while resting, usually at night or early morning) (Prinzmetal angina), loss of coordination, difficulty in speaking, dry skin, migraine, visual disturbances or double vision, ringing in the ears, dizziness on standing up (especially when getting up from a sitting or lying position), increased need to pass water at night, pain, 'flu-like' symptoms, sleepiness, widening of blood vessels, inflammation of the large bowel (signs include: diarrhoea, usually with blood and mucus, stomach pain, fever), inflammation of the stomach (signs include: pain, nausea, vomiting), area of abnormal density in the lung, increased creatinine level in blood tests, which may be a sign of kidney problems.

The following side effects have been reported but it is not known exactly how often they occur:
- Potentially life-threatening, irregular heartbeat (Torsade de pointes);
- Inflammation of the liver, symptoms include nausea, vomiting, itching, yellowing of the skin and eyes, discoloration of stool and urine (hepatitis);
- Lung inflammation (signs include fever, coughing, difficulty breathing, wheezing; which causes scaring of the lungs) (allergic alveolitis, including interstitial lung disease, pneumonitis);
- Inflammation of the kidneys (tubulointerstitial nephritis).
- Stroke (see section 2).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Anagrelide Viatris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

If your doctor stops your medicine, do not keep any leftover capsules unless your doctor tells you to. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Anagrelide Viatris contains
The active substance is anagrelide. Each capsule contains anagrelide hydrochloride monohydrate equivalent to 1 mg anagrelide.

The other ingredients are lactose, croscarmellose sodium, povidone, microcrystalline cellulose, magnesium stearate, gelatin, titanium dioxide (E171) and iron oxide black (E172). See section 2 'Anagrelide Viatris contains lactose and sodium'.

What Anagrelide Viatris looks like and contents of the pack
Anagrelide Viatris 1 mg hard capsules have a grey body and cap. The capsule is filled with a white to off-white powder.
The capsule size is approximately 14.3 x 5.3 mm.

Anagrelide Viatris is available in plastic bottles of 30 ml or 75 ml with a tamper evident, child-resistant closure and a desiccant. Each bottle contains 100 hard capsules.

Marketing Authorisation Holder
Viatris Limited
Damastown Industrial Park
Mulhuddart, Dublin 15
DUBLIN
Ireland

Manufacturer
Synthon Hispania SL
C/ Castelló no1
POL. Las Salinas
Sant Boi de Llobregat
08830 Barcelona
Spain

Synthon BV
Microweg 22
6545 CM Nijmegen
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Viatris
Tél/Tel: + 32 (0)2 658 61 00

България
Майлан ЕООД
Тел: +359 2 44 55 400

Česká republika
Viatris CZ s.r.o.
Tel: + 420 222 004 400

Danmark
Viatris ApS
Tlf: +45 28 11 69 32

Deutschland
Viatris Healthcare GmbH
Tel: +49 800 0700 800

Eesti
Viatris OÜ
Tel: + 372 6363 052

Ελλάδα
Viatris Hellas Ltd
Τηλ: +30 2100 100 002

España
Viatris Pharmaceuticals, S.L.
Tel: + 34 900 102 712

France
Viatris Santé
Tél: +33 4 37 25 75 00

Hrvatska
Viatris Hrvatska d.o.o.
Tel: +385 1 23 50 599

Ireland
Viatris Limited
Tel: +353 1 8711600

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Viatris Italia S.r.l.
Tel: + 39 (0) 2 612 46921

Lietuva
Viatris UAB
Tel: +370 5 205 1288

Luxembourg/Luxemburg
Viatris
Tél/Tel: + 32 (0)2 658 61 00
(Belgique/Belgien)

Magyarország
Viatris Healthcare Kft.
Tel.: + 36 1 465 2100

Malta
V.J. Salomone Pharma Ltd
Tel: + 356 21 22 01 74

Nederland
Mylan BV
Tel: + 31 (0)20 426 3300

Norge
Viatris AS
Tlf: + 47 66 75 33 00

Österreich
Viatris Austria GmbH
Tel: +43 1 86390

Polska
Viatris Healthcare Sp. z o.o.
Tel.: + 48 22 546 64 00

Portugal
Mylan, Lda.
Tel: + 351 214 127 200

România
BGP Products SRL
Tel: +40 372 579 000

Slovenija
Viatris d.o.o.
Tel: + 386 1 23 63 180

Slovenská republika
Viatris Slovakia s.r.o.
Tel: +421 2 32 199 100

Suomi/Finland
Viatris Oy
Puh/Tel**:** +358 20 720 9555

Κύπρος
CPO Pharmaceuticals Limited
Τηλ: +357 22863100

Latvija
Viatris SIA
Tel: +371 676 055 80

Sverige
Viatris AB
Tel: +46 (0)8 630 19 00

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.