VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Essential thrombocythaemia (ET) is a condition which occurs when the bone marrow produces too many blood cells, known as platelets, causing serious problems with blood circulation and clotting. The incidence of ET in the general population is 1 to 2.5 per 100,000 individuals annually. Essential thrombocythaemia is primarily diagnosed in older patients between 50 to 60 years of age. There also appears to be a second peak of patients diagnosed at around age 30, with the majority being females. Essential thrombocythaemia occurs more often in females than in males (approximately 2-fold higher) and, therefore, ET-associated pregnancies are commonly observed. Major thrombosis (blood clotting complications) concurrently occurs in patients with ET and is associated with a significant death rate. Patients with ET have shortened 5- and 10-year survival rates when compared to the general population. **[Sanchez S and Ewton A, 2006; Reilly JT, 2012]**

VI.2.2 Summary of treatment benefits

No pivotal clinical efficacy and safety studies were conducted for Anagrelide hydrochloride 0.5 mg hard capsule considering this is a generic product. The available medical literature is considered sufficient to evaluate the safety of Anagrelide hydrochloride 0.5 mg hard capsule in the proposed therapeutic indication.

VI.2.3 Unknowns relating to treatment benefits

Limited data are available on the use of anagrelide in the paediatric population. There are no adequate data from the use of anagrelide in pregnant women. It is not known whether anagrelide is excreted in human milk or not. No human data on the effect of anagrelide on fertility are available.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	What is known	Preventability
Heart related effects (abnormal ECG changes, severe problem with the rate or rhythm of the heartbeat, heart muscle disease, enlarged heart, and congestive heart failure)[Cardiac events (QT prolongation, ventricular tachycardia, cardiomyopathy,	Adverse events related to the heart such as abnormal ECG changes, severe problem with the rate or rhythm of the heartbeat, heart muscle disease, enlarged heart and congestive heart failure have been reported with anagrelide use. Cytochrome P450 1A2 (abbreviated CYP1A2) is a member of the cytochrome P450, which is involved in	Yes. Patients should inform their treating doctor if they have or think they might have a heart problem, if they were born with or have a family history of prolonged abnormal ECG, or are taking other medicines that result in abnormal ECG changes, or if they have low levels of electrolytes (minerals present in

cardiomegaly and congestive heart failure)]	the breakdown of most medications. Anagrelide blocks the enzyme cyclic AMP phosphodiesterase III, and because of its ability to increase heart rate and produce strong muscle contraction, it should be used with care in patients of any age group with known or suspected heart disease and those taking medicines used to treat heart disorders, e.g., milrinone, enoximone, amrinone, olprinone, and cilostazol. Moreover, serious heart related adverse events have also occurred in patients without suspected heart disease and with a normal pre-treatment cardiovascular examination. Severe problems with the rate or rhythm of the heart beat (ventricular tachycardia) and congestive heart failure are uncommon (may affect up to 1 in 100 people), and heart muscle disease (cardiomyopathy), and an enlarged heart (cardiomegaly) are rare (may affect up to 1 in 1,000 people) side effects reported with anagrelide use. Anagrelide should only be used if the potential benefits of therapy outweigh the potential harm.	blood), e.g., potassium, magnesium, or calcium. Before starting treatment with anagrelide, a cardiovascular examination, including a baseline ECG and echocardiography, are recommended for all patients. 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 laboratory tests. Patients with low potassium levels (hypokalaemia) or low magnesium levels (hypomagnesaemia) must be treated in order to obtain normal levels before starting anagrelide treatment, and these electrolytes should be monitored periodically during therapy. Patients are advised to inform their treating doctor or pharmacist if they are taking or have recently taken the following medicines: Medicines that can alter heart rhythm; e.g., sotalol, amiodarone. Medicines used to treat heart disorders, e.g., milrinone, enoximone, amrinone, olprinone, and cilostazol.
Drug interaction with inhibitors of platelet	Acetylsalicylic acid is a substance present in many medicines used to relieve pain and lower fever, as	Yes. Before starting treatment with anagrelide, the patient is advised

aggregation (acetylsalicylic acid)	well as to prevent blood clotting, also known as aspirin. At the doses recommended for use in the treatment of ET, anagrelide may enhance the effects of acetylsalicylic acid. Use of simultaneous anagrelide and acetylsalicylic acid has been associated with major haemorrhagic events (bleeding).	to inform their treating doctor or pharmacist if they are taking or have recently taken acetyl salicylic acid.

Use in patients with moderate or severe liver impairment (use in patients with moderate or severe hepatic impairment)	Anagrelide should not be used in patients with moderate or severe liver failure. Liver metabolism represents the major route of anagrelide clearance; therefore patients with liver function problems are expected to have more anagrelide exposure, which could increase the risk of abnormal changes on ECG. It is therefore recommended that patients with moderate or severe liver problems not take anagrelide. Anagrelide is not recommended in patients with elevated transaminases (>5 times the upper limit of normal) (range for normal AST is between 10 to 40 units per litre and for ALT is between 7 to 56 units per litre). Elevated alanine transaminase and aspartate transaminase may be an indicator of liver damage. Before starting treatment with anagrelide, the potential harm and benefits of anagrelide therapy should be judged in patients with liver failure.	Yes. Patients should inform their treating doctor if they are suffering from liver problems. Close monitoring is required for patients undergoing a liver function test [check liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST)].

Use in patients with moderate or severe kidney impairment (creatinine clearance less than 50 ml/min) [use in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min)]	Patients with moderate or severe kidney problems (creatinine clearance less than 50 ml/min) should not take anagrelide. Before starting treatment with anagrelide, the potential harm and benefits of anagrelide therapy should be judged in patients with kidney failure.	Yes. Close monitoring is required for patients undergoing a kidney function test (serum creatinine and urea). This test is performed in order to check whether the kidneys are working properly or not. Patients should inform their treating doctor if they are having kidney problems.

Important potential risks:

Not applicable

Missing information:

Risk	**What is known**
Use during pregnancy and breast-feeding (exposure during pregnancy and lactation)	No sufficient information is available regarding the use of anagrelide in pregnant women. Studies in animals have shown reproductive toxicity. The potential harm for humans is unknown; therefore anagrelide is not advised during pregnancy. Patients should inform their treating doctor if they are pregnant or are planning to become pregnant. If anagrelide is used during pregnancy, or if the patient becomes pregnant while using the medicinal product, they should be advised of the potential harm to the unborn baby (foetus). Anagrelide or its metabolites may or may not pass on to the new-born baby/infant from the milk of the breast-feeding mother taking anagrelide. Since it is unknown whether anagrelide or its metabolites are passed in human milk, breast-feeding should be discontinued during treatment with anagrelide.
Use in paediatric population	The safe and effective use of anagrelide in children has not been known. The experience in children and adolescents is very limited; anagrelide should be used with care in this patient population. Cytoreductive therapy (therapy with the intention of reducing the number of cells in a lesion, usually cancerous cells) is typically considered in high risk paediatric patients. Discontinuation of treatment should be

Risk	What is known
	considered in paediatric patients who do not have a satisfactory treatment response after approximately three months.
Effect of drug on the individual's ability to reproduce (effect on 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, when using doses in excess of the normal range, anagrelide disrupted implantation (complications observed during the early stage of pregnancy).

VI.2.5 Summary of additional risk minimisation measures by safety concern

The Summary of Product Characteristics (SPC) of Anagrelide 0.5 mg hard capsules provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PIL). All these risk minimisation measures are given in SPC and PIL of Anagrelide 0.5 mg hard capsules.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post authorisation study is planned for this product.

VI.2.7 Summary of changes to the Risk Management Plan over time

This is the first RMP for Anagrelide 0.5 mg hard capsules.