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 individual annually. ET 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 majority of females. ET occurs more often in females than in males (approximately two-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 significant death rate. Patients with ET have shortened 5- and 10-year survival rates when compared to general population.

VI.2.2 Summary of treatment benefits

Anagrelide was effective in lowering platelet counts in four main studies involving patients with various diseases in which the bone marrow produces too many cells. Almost 3,000 of the patients in the studies had essential thrombocythaemia, defined as a platelet count of more than 600 million/ml. Most patients had previously received other medicines but needed to change treatment. Anagrelide was not compared with any other medicines. Patients were treated with anagrelide for up to five years. The main measure of effectiveness was the number of patients who had a ‘complete response’, defined as a reduction in platelet counts of at least 50% from the start of treatment or to below 600 million/ml.

In the largest study, 67% of the patients with essential thrombocythaemia (628 out of 934), and 66% of those who could not tolerate or did not respond to other treatments (480 out of 725) had a complete response to anagrelide. In the other three studies, the percentage of patients with a complete response ranged from 60% to 82%.

VI.2.3 Unknowns relating to treatment benefits

Limited data are available on the use of anagrelide in the paediatric population, in patients with renal impairment and population, in patients with hepatic impairment. 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.

VI.2.4 Summary of safety concerns

Table 9: Important Identified Risk(s)

Risk(s)	What is known	Preventability
Heart problems like: Awareness of a forceful heartbeat which may be rapid or irregular; Abnormally rapid heartbeat; Inability of heart to pump sufficient blood; Abnormally rapid heartbeat due to disturbance in ventricles of heart; Heart muscle diseases like cardiomegaly and cardiomyopathy.	Serious heart problems like palpitation, tachycardia, ventricular tachycardia, cardiomyopathy, cardiomegaly and congestive heart failure have been reported during clinical trials and other safety studies with anagrelide. Clinical studies were conducted to evaluate effect of anagrelide on heart which indicated that anagrelide caused tachycardia and prolongation in QT interval (seen on ECG, electrical recording of the heart suggestive). Patients over 60 years of age have twice the incidence of heart problems. There are more chances of these heart problems in patients with heart disease; however, serious heart problems have been observed in patients of any age with or without heart disease.	Yes, before starting treatment, the patient should inform the treating physician if he/she had or is suffering from any heart related problem, if he/she was born with or have family history of prolonged QT interval, or is taking other medicines that result in abnormal ECG changes or if has low levels of electrolytes e.g. potassium, magnesium or calcium. Laboratory tests to measure the function of heart, including ECG and echocardiography, should be performed before starting treatment. During treatment, ECG and tests to measure electrolytes level (potassium, magnesium and calcium) should be performed at regular interval in order to examine function of heart.
Drug interaction with inhibitors of platelets aggregation (acetylsalicylic acid)	Acetylsalicylic acid is a substance present in many medicines used to relieve pain and lower fever, as 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).	Yes. Before starting treatment with anagrelide, the patient is advised 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 insufficiency (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	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)].

Risk(s)	What is known	Preventability
	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.	
Use in patients with moderate or severe kidney insufficiency (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 Risk(s)

Not applicable

Table 10: Missing Information

Risk(s)	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

Risk(s)	What is known
	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 children (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 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 risk minimisation measures by safety concern

Summary of Product Characteristics (SmPC) of Anagrelide hydrochloride 0.5 mg hard capsule 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 (PL). All these risk minimization measures are given in SmPC and PL of Anagrelide hydrochloride 0.5 mg hard capsule. This medicine has no additional risk minimization measures for any of mentioned safety concerns.

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

The summary of RMP changes are presented in the below table.

Version	Date	Safety Concerns	Comments
V1.0	15-Nov-2016	**Important identified risks:** 1. Cardiac disorders (Palpitations, Tachycardia, Congestive heart failure, Ventricular tachycardia, Cardiomegaly, Cardiomyopathy, Torsade de pointes)	First version of the RMP.

Version	Date	Safety Concerns	Comments
		2. Nervous system disorders (Headache, dizziness) 3. Anaemia 4. Fluid retention 5. Gastrointestinal disorders (Nausea, Diarrhoea, Abdominal pain, Flatulence, Vomiting) **Important potential risks:** 1. Use in patients with renal impairment 2. Use in patients with hepatic impairment 3. Use in paediatric population 4. Use during pregnancy **Missing information:** 1. Use in lactation	
V1.1	02-June-2017	**Important identified risks:** 1. Cardiac events (QT prolongation, torsade de pointes, ventricular tachycardia, cardiomyopathy, cardiomegaly and congestive heart failure) 2. Drug interaction with inhibitors of platelets aggregation (acetylsalicylic acid) 3. Use in patients with moderate or severe hepatic impairment 4. Use in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min) **Important potential risks:** 1. Lack of efficacy/ Thrombohaemorrhagic events 2. Benign or malignant neoplasms including myelofibrosis 3. Interstitial lung disease **Missing information:** 1. Exposure during pregnancy and lactation 2. Use in paediatric population 3. Effects on fertility	List of safety concerns updated based on RMS and CMS comments. Information regarding the updated safety concerns aligned to respective sections of the RMP. Revised based on updated Glenmark template.
V1.2	13-Oct-2017	**Important identified risks:** 1. Cardiac events (QT prolongation, ventricular tachycardia, cardiomyopathy, cardiomegaly and congestive heart failure) 2. Drug interaction with inhibitors of platelets aggregation (acetylsalicylic acid) 3. Use in patients with moderate or severe hepatic impairment 4. Use in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min)	List of safety concerns updated based on RMS comments. Information regarding the updated safety concerns aligned to respective sections of the RMP.

Version	Date	Safety Concerns	Comments
		Important potential risks: Not applicable **Missing information:** 1. Exposure during pregnancy and lactation 2. Use in paediatric population 3. Effects on fertility	