## VI.2 Elements for a public summary

### VI.2.1 Overview of disease epidemiology

Essential thrombocythaemia is a medical condition in which increased amounts of blood components called platelets are present in the blood; the term 'essential' means that the disease has no obvious cause (11). Too many platelets circulating in the blood can cause blood clots to form spontaneously, blocking the flow of blood through blood vessels (7). Symptoms may include redness and warmth of hands and feet, often with burning pain, tingling and other abnormal sensations in the fingertips, hands, and feet, chest pain, loss of vision or seeing spots, headache, weakness, dizziness and bleeding (usually mild) (7). The spleen and liver may enlarge (7). Although approximately half of the patients do not experience any symptoms, treatment is considered required for those at risk for more serious complaints (1, 2).

Essential thrombocythaemia is a rare disease. Annually, worldwide approximately one in 100,000 people are newly diagnosed with the disease (12). In the United States, it was estimated that between 2008 and 2010 approximately 38-57 people every 100,000 patients suffered from essential thrombocythaemia (5).

### VI.2.2 Summary of treatment benefits

Current therapy strategies for essential thrombocythaemia include (1-3):

- Observation (no medicinal treatment);
- Low-dose aspirin for low-risk essential thrombocythaemia patients;
- Therapy to reduce the number of platelets is used in high-risk essential thrombocythaemia patients. Hydroxyurea is the first choice of treatment. When insufficient results are obtained with hydroxyurea or if hydroxyurea is not well tolerated, anagrelide can be prescribed (second choice treatment). Pregnant patients are treated with interferons.

High-risk patients are patients over the age of 60 years and/or with high platelet levels in the blood and/or with a history of bleeding and clotting problems (1, 10, 11).

Anagrelide has been studied in four main studies and on approximately 3,000 patients with essential thrombocythaemia. The majority of these patients had received medicinal treatment before, but had to switch treatment. Treatment with anagrelide was provided for up to five years. Anagrelide showed to be effective in lowering the number of platelets in the blood. Whether patients experienced sufficient benefit from decreased bleeding and clotting problems was not convincingly shown (10, 11).

### VI.2.3 Unknowns relating to treatment benefits

There is not enough information available on the use of anagrelide in:
- Children and adolescents;
- Patients who plan to have children.

### VI.2.4 Summary of safety concern

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Heart conditions occurring in patients aged 50 years and under. | During treatment with anagrelide serious heart conditions may occur.<br>Although a higher incidence of cardiac events has been observed in patients over 60 years of age, care should be taken in patients with a higher maximum plasma concentration of active anagrelide (age range 22 - 50 years).<br>While some heart conditions (*e.g.* rapid or irregular heart beat) may affect up to one in 10 people taking anagrelide, others may affect up to one in 100 people (*e.g.* ventricular tachycardia and heart failure) or up to one in 1,000 people (*e.g.* cardiomyopathy, cardiomegaly and heart attack). | Patients should discuss with their treating doctor before initiating anagrelide, if they think they may have a heart problem.<br>In addition, the doctor may perform an examination of heart and blood vessels prior to initiating treatment with anagrelide. The doctor should also monitor for potential effects on heart and vessels during treatment with anagrelide. |
| Particular disorder of the heart's electrical activity (QT prolongation) and a specific type of abnormal heart rhythm that can lead to sudden cardiac death | During treatment with anagrelide serious heart conditions may occur.<br>The incidence of QT syndrome is not known; however, patients | Patients should discuss with their treating doctor before initiating anagrelide, if :<br>- They were born with or have a family history of prolonged QT |

| Risk | What is known | Preventability |
|---|---|---|
| (Torsade de pointes). | who are born with prolonged QT syndrome, who in the past have suffered from prolonged QT interval, who are taking medicines which can prolong the QT interval or who have low potassium levels in their blood, are at increased risk of developing prolonged QT interval when taking anagrelide.<br><br>Torsade de pointes is a side effect that has been observed during treatment with anagrelide, although it is unknown how often it occurs. | interval (seen on an electrical recording of the heart, ECG);<br>- They are taking medicines that could affect the heart and result in abnormal ECG changes;<br>- They have low levels of blood potassium, magnesium or calcium.<br><br>The doctor should test the levels of potassium, magnesium and calcium in the blood of patients, before and during treatment with anagrelide.<br><br>In addition, the doctor may perform an examination of heart and blood vessels prior to initiating treatment with anagrelide. The doctor should also monitor for potential effects on heart and vessels during treatment with anagrelide. |
| Use of anagrelide in combination with acetylsalicylic acid, a substance used to prevent blood clotting, also known as aspirin. | Anagrelide affects the number of platelets, blood cells involved in blood clotting.<br><br>Bleeding can therefore occur during treatment with anagrelide, especially when used together with other medicines that can "make the blood thinner", such as aspirin. Bleeding can manifest in different organs, varying from bruising, nosebleeds, bleeding of gums to serious bleeding of the digestive tract. | Patients should inform their treating doctor of other medicines used.<br><br>The doctor should evaluate the possible risks in the context of possible benefits before initiating anagrelide as a combined treatment with aspirin. |
| Use in patients with moderate or severe liver problems (hepatic impairment). | Limited data is available regarding the treatment with anagrelide of patients with liver problems. However, given that | Patients with moderate or severe liver problems should not be treated with anagrelide. |

| Risk | What is known | Preventability |
|---|---|---|
| | the liver is the main organ responsible for "inactivating" (metabolising) anagrelide after a certain amount of time that it is in the body, if the liver does not work properly, it can be that patients taking anagrelide have in their body an amount of "active medicine" higher than expected, which could lead to increased side effects including increases in liver enzymes in the blood and hepatitis.<br>The seriousness of such side effects can vary from an asymptomatic mild course to development of liver damage. | Before initiating anagrelide treatment, the treating doctor should evaluate the potential risks and benefits of anagrelide therapy in a patient with mild liver problems.<br>The doctor should test the levels of liver enzymes in the blood of patients, before and during treatment with anagrelide.<br>Patients should immediately inform their doctor or pharmacist if they get symptoms of inflammation of the liver (hepatitis) such as: nausea, vomiting, itching, and yellowing of the skin and eyes or discoloration of stool and urine. |
| Use in patients with moderate or severe kidney problems (renal impairment). | Limited data is available regarding the treatment with anagrelide of patients with moderate or severe kidney problems.<br>Increased levels of blood creatinine (creatinine increases when the kidneys are not functioning properly) and kidney failure may affect up to one in 1,000 people during treatment with anagrelide.<br>The seriousness of the condition can vary from having no symptoms to the development of severe kidney damage. | Patients with moderate or severe kidney problems should not be treated with anagrelide.<br>Before initiating anagrelide treatment, the treating doctor should evaluate the potential risks and benefits of anagrelide therapy in a patient with mild kidney problems.<br>Patients should discuss with their treating doctor pre-existing kidney problems before initiating anagrelide.<br>The doctor should regularly perform blood tests in patients before and during treatment with anagrelide, to check if their kidneys are working well. |

**Important potential risks**

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| Cancerous or non-cancerous cell proliferations (including an uncommon type of chronic blood and bone marrow cancer leading to the over- or underproduction of various blood cells [myelofibrosis]) | Essential thrombocythaemia may progress to blood and bone marrow cancer including myelofibrosis (*i.e.* an uncommon type of chronic blood and bone marrow cancer leading to the over- or underproduction of various blood cells) (8) and acute myeloid leukaemia (*i.e.* a life-threatening disorder in which immature cells rapidly accumulate in the bone marrow, destroying and replacing cells that produce normal blood cells) (6). The speed of disease progression is not known. However, given that children have a longer disease course, they may be at greater risk for developing blood and bone marrow cancer, relative to adults. In addition, non-hematologic cancers have been observed in a study conducted in rats: uterine cancer was found in female rats and tumours of the adrenal glands (phaeochromocytoma) were observed both in male and female rats (10).<br><br>Children should be monitored regularly for disease progression according to standard clinical practices, such as physical examination, assessment of relevant disease markers and examination of collected bone marrow samples (biopsy) (4). |
| Use in pregnant women | There is no adequate data on the use of anagrelide in pregnant women. The patient should inform their treating doctor when pregnant or if pregnancy is planned. Effective contraception should be used when taking anagrelide if a risk of becoming pregnant exists. Furthermore, it is not known if anagrelide can be passed to the baby via breast milk.<br><br>Pregnant women and women who are breast-feeding should not take anagrelide.<br><br>Studies in laboratory animals with extremely high dose of anagrelide have shown toxic effects on the unborn pups. However, since these results were achieved with very high drug doses the relevance for use in humans is unknown. |
| A large group of diseases that inflames or scars the lungs (interstitial lung disease) | Interstitial lung disease is a side effect that has been observed during treatment with anagrelide, although it is unknown how often it occurs. Because interstitial lung disease can cause symptoms that are similar to those of much more common disorders, such as pneumonia or chronic obstructive pulmonary disease, it may not be suspected at first. Therefore, patients who experience signs of lung inflammation (including fever, coughing, difficulty breathing, wheezing) should talk to their prescribing |

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| | doctor or pharmacist (9). |
| Lack of efficacy for conditions involving blood clotting or bleeding (thrombohaemorrhagic events) | Clinical benefit for conditions involving blood clotting or bleeding (thrombohaemorrhagic events: *e.g.* heart attack or stroke) has not been convincingly demonstrated. |

**Missing information**

| Risk | What is known |
|---|---|
| Effects on fertility | There are no patient data on the effect of anagrelide on fertility.<br>In male laboratory animals, there was no effect on fertility or reproductive performance with anagrelide.<br>In female laboratory animals, very high doses of anagrelide interfered with the first stages of pregnancy (implantation). |
| Use in children and adolescents (paediatric patients) | Very limited data is available regarding the treatment of children and adolescents with anagrelide. Therefore, the correct dosage of anagrelide for these patients is not known.<br>Studies on the use of anagrelide in very few paediatric patients with essential thrombocythaemia did not show any new safety issue (compared to adult patients).<br>The doctor should be very careful when treating children and adolescents with anagrelide. |

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

No additional risk minimisation measures have been proposed.

### VI.2.6 Planned post authorisation development plan

No post-authorization development is planned.

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

Not applicable.