RISK MANAGEMENT PLAN (RMP)

Active substance:	Anagrelide hydrochloride.
Pharmacotherapeutic group	Other antineoplastic substances. (ATC Code L01XX35).
Marketing Authorisation Holder or Applicant:	AOP Orphan Pharmaceuticals AG Wilhelminenstr. 91/ II f 1160 Vienna, Austria
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Thromboreductin®, Anagrelide AOP 0,5 mg capsules
Data lock point for this RMP:	30 September 2016
Version number:	01
Date of final sign off:	29 January 2018

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Essential thrombocythaemia (ET) is a rare chronic blood disorder characterised by the overproduction of blood cells known as platelets in the bone marrow. Roughly 10 to 40 people out of 100,000 have this disease and roughly one person out of 100,000 are newly diagnosed with ET each year (this number is even lower for children). 'Essential' means that the disease has no obvious cause. Large numbers of platelets in the blood can cause serious problems with blood circulation and clotting.

VI.2.2 Summary of treatment benefits

Thromboreductin® is a medicine used to reduce the number of platelets (components that help the blood to clot) in patients with essential thrombocythaemia (ET). Thromboreductin contains the active substance anagrelide. By reducing the number of platelets in these patients, serious health problems such as a heart attack or stroke can be prevented. In five clinical studies, 307 patients with ET were treated with Thromboreductin for one year. Further, a patient registry collected information from 722 ET patients who were treated with Thromboreductin over five years. The main measure of effectiveness was the number of patients who had a reduction in platelet count to below 600 million/ml. In the largest study, more than 65% of the patients with ET, had a platelet count below 600 million/ml in response to Thromboreductin treatment.

VI.2.3 Unknowns relating to treatment benefits

Thromboreductin® has not been adequately studied in children for the reduction of an increased platelet number. There have been no trials in pregnant or breast-feeding women due to safety reasons and Thromboreductin® should not normally be used by these women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Cardiac events in young patients (age 50 years and under)	Cardiac complications with Thromboreductin® can occur in any patient of any age, with or without pre-existing cardiac disease.	Thromboreductin® should be used with caution in patients of any age with known or suspected heart disease. A cardiovascular examination before treatment and monitoring during treatment for evidence of cardiovascular effects is recommended.
Cardiac events related to heart rhythm disorders ("QTc interval prolongation" and "Torsade de Pointes")	Heart rhythm disorders can cause severe heart problems (e.g. sudden cardiac death, ventricular arrhythmias).	Thromboreductin® should be used with caution in patients who have family history of prolonged QT interval or who take other medicines that result in abnormal ECG changes or who have low levels of electrolytes, e.g., potassium, magnesium or calcium. A pre-treatment cardiovascular examination and monitoring during treatment for evidence of cardiovascular effects is recommended.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Benign or malignant abnormal growth of tissue (neoplasms)	Essential thrombocythaemia can, if not treated properly (e.g., with anagrelide), develop into cancer (i.e., white blood cell cancer called "leukaemia" or bone marrow cancer called "myelofibrosis"). In some cases, however, the formation of neoplasms were observed during the treatment with anagrelide. It is suggested that abnormal growth of tissue observed in patients treated with anagrelide is a consequence of the natural history of essential thrombocythaemia rather than a result of anagrelide treatment.

Risk	What is known (Including reason why it is considered a potential risk)
Lung diseases affecting the tissue and space around the air sacs of the lungs (Interstitial lung disease)	Prolonged interstitial lung disease may result in pulmonary fibrosis which is a respiratory disease in which scars are formed in the lung tissues, leading to serious breathing problems. Hypoxia (inadequate oxygen supply at the tissue level) caused by pulmonary fibrosis can lead to pulmonary hypertension, which, in turn, can lead to heart failure.
Thrombohaemorrhagic events	A thrombohaemorrhagic event is a process that involves either a blood clot or bleeding, such as a heart attack or stroke which are life threatening conditions.
Influence of medicinal products that - Affect the clearance of anagrelide - Have cardiovascular effects - Affect platelet function	Concomitant use of medicinal products which affect the clearance of anagrelide, have effects on the cardiovascular system or affect the platelet function, may intensify and or prolong the action of anagrelide in the body.
Exposure during pregnancy	There are limited data in humans regarding administration during pregnancy. Studies in animals have shown harm to the foetus at very high dosages. Therefore, anagrelide is not recommended during pregnancy.

Missing information

Risk	What is known
Use in the paediatric population	Limited data are available on the treatment of anagrelide in the paediatric population.
Use in hepatic impaired patients	Patients with hepatic impairment may have reduced hepatic clearance for anagrelide. Due to the limited amount of data in this patient population, treatment with anagrelide in patients with moderate or severe hepatic impairment is contraindicated.
Use in renal impaired patients	Due to the limited amount of data in this patient population, treatment with anagrelide in patients with moderate and severe renal impairment is contraindicated.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which 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). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

There are no studies planned.

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

Not applicable.