PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ICLUSIG (PONATINIB)

This is a summary of the RMP for Iclusig. The RMP details important risks of Iclusig, how these risks can be minimised, and how more information will be obtained about Iclusig's risks and uncertainties (missing information).

Iclusig's SmPC and its PL give essential information to HCPs and patients on how Iclusig should be used.

This summary of the RMP for Iclusig should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Iclusig's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Iclusig is authorised for use in adult patients with CML and Ph+ ALL (see SmPC for the full indication). It contains Ponatinib as the active substance and it is given by either 45 mg, 30 mg or 15 mg film-coated tablets once daily.

Further information about the evaluation of Iclusig's benefits can be found in Iclusig's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/iclusig).

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Iclusig, together with measures to minimise such risks and the proposed studies for learning more about Iclusig 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of Iclusig are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Iclusig. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 19: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Serious Infections Vascular occlusion events, comprising: • Arterial Occlusive Events (AOEs) o Cardiac Arterial Occlusive events o Cerebral Arterial Occlusive events o Peripheral Vascular Arterial Occlusive events o Retinal Arterial Occlusive events and Vision Loss • Venous Thrombotic/Embolic Events (VTEs) o Retinal Vein Thrombotic events and Vision Loss
Important potential risks	Teratogenicity
Missing information	None

II.B Summary of Important Risks

Table 20: Summary of Important Identified Risk Serious Infections

Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	Clinical studies and post-marketing data
Risk factors and risk groups	Patients with leukemias typically are affected by nuisance infections due to the underlying hematologic condition. With active treatment, particularly those agents that cause defects in cell-mediated immunity, the incidence of opportunistic infections increases, although endogenous bacterial, mycobacterial, and fungal infections also occur (Young, 2011).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 and PL section 4. Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Table 21: Summary of Important Identified Risk Vascular Occlusion Events

Important Identified Risk: Vascular occlusion events	
Evidence for linking the risk to the medicine	Clinical studies and post-marketing data
Risk factors and risk groups	Risk factors for each category of vascular occlusion are given below, and include prior history of an event, hypertension, diabetes, smoking, hypercholesterolemia, and family history. A recent study suggests that the generation of NETs may be a mechanism by which cancers are prothrombotic (Demers et al 2012). NETs are associated with bacterial killing (Brinkmann et al, 2004), and, more recently, with thrombotic processes (Fuchs et al, 2010, Brill et al, 2012). The authors demonstrated that neutrophils from mice with CML-like myeloproliferative neoplasia generated NETs in vivo. When neutrophils were isolated and stimulated in vitro with platelet-activating factor, they generated NETs to a degree higher than would be predicted by the percentage of BCR-ABL1+ neutrophils, with in vitro imatinib or dasatinib having no effect on the rate of NET formation. The authors suggest that some systemic aspect of CML may be stimulating NET formation. If true, it suggests that CML itself is prothrombotic, and the property may not be sensitive to TKIs. VOEs, especially AOEs, have also emerged as important identified risks associated with the use of other TKIs, including dasatinib and nilotinib (Valent et al, 2014) (Douxfils et al, 2016).

Important Identified Risk: Vascular occlusion events	
	In the phase 2 trial, almost half of the patients who were reported to have a treatment-emergent AOE were ≥65 years old (47/104 patients; 45.19%) and more than half were male (62/104 patients; 59.62%), a majority of the patients who were reported to have risk factors for AOEs or serious AOEs had >1 risk factor (86/104 [82.7%] and 70/83 [84.3%], respectively). The most common risk factors observed in patients who were reported to have an AOE were hypertension (75/104 patients; 72.12%), hypercholesterolemia (69/104 patients; 66.35%), and history of cardiac disease (53/104 patients; 51.0%). History of ischemic disease, diabetes, and obesity also were reported in relation to the occurrence of AOEs in >10% of the patients with any risk factors. Of patients who were reported to have no risk factors by medical history, age, or sex, 2/104 patients (1.9%) were reported to have a non-serious treatment emergent AOE and 1 patient (1.2%) was reported to have a serious AOE. **Arterial Occlusive Events** **Cardiac AOEs** Risk factors that promote heart disease include economic transition, urbanization, industrialization, and globalization. Therefor lifestyle changes promote heart disease. Further general risk factors include tobacco use, physical inactivity, and unhealthy diet. Newly emerging CVD risk factors such as low birth weight, folate deficiency and infestations are more frequent among the poorest in low- and middle-income countries (The National Academies. Promoting Cardiovascular Health in the Developing World (2010)). Elderly patients and patients with underlying pre-disposing disease such as diabetes mellitus seemed to be at higher risk of developing ischaemic cardiac side effects during TKI therapy. In the phase 2 trial, patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion AEs were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia. Of the 56 patients with a cardiac ischemic event, 32 (57.1%) patients did present with a history of cardiac disease. **Cerebral AOEs** There were 28 patients without a history of ischemic cerebrovascular disease who experienced a serious cardiac ischemic/thrombotic event. Risk factors include heart disease (eg, atrial fibrillation, valvular disease, recent MI (Wein and Bornstein 2000; Di Tullio and Homma 2002), hypertension (MacMahon et al 1990), smoking (Kawachi et al 1993), diabetes (Karapanayiotides et al 2004), and hypercholesterolemia). Previous transient ischemic attack is a strong predictor of future stroke.

Important Identified Risk: Vascular occlusion events	
	In the phase 2 trial, of the 39 patients with an AOE, 20 (51.3%) of patients presented with a history of ischemic disease and 12 (30.8%) presented with a history of diabetes. **Peripheral Vascular AOEs** Risk factors contributing to PVD include individuals who are ≥ 50 years of age with diabetes mellitus, smoking >10 pack-year/history of smoking (Hirsch et al 2001). PVD is more prevalent among families with atherosclerosis and in those with risk factors for cardiovascular disease, men, and certain ethnic populations. Many risk factors of PVD are similar to those that are associated with coronary atherosclerosis and include smoking, hypertension, diabetes, hyperlipidemia, homocysteinemia, metabolic syndrome, including inflammatory mediators (Selvin and Erlinger, 2004; Smith et al, 2004; Murabito, 1997). In the phase 2 trial, of the 40 patients with a peripheral vascular AOE, 15 (37.5%) of patients presented with a history of ischemic disease and 11 (27.5%) with a history of diabetes. About 90% of patients with renal artery stenosis have atherosclerosis as a predisposing factor; 10% of patients with renal artery stenosis have fibromuscular dysplasia as a predisposing factor. Atherosclerotic renal artery stenosis is a common condition that typically occurs in patients at high risk of cardiovascular disease with coexistent vascular disease at non-renal sites (Cheung et al, 2005). **Venous Thrombotic/Embolic Events** In the phase 2 study, with longer follow-up it has also become evident that VTEs are largely observed early in the course of therapy. The possible reasons include the initial active malignancy or acquired risk factors that may occur early in the course of therapy, including immobility, trauma, surgery, and hospitalization, all of which exacerbate blood stasis in a hyperviscous state such as an active malignancy Ku and colleagues studied risk factors among patients with acute leukemia (2009). They found that the 2-year incidence of venous thromboembolism in 2482 patients ALL was 4.5%. Blann and Dunmore (2011) found an association of both arterial and venous thrombosis with various types of cancer. **Retinal Vascular Occlusive Events and Vision Loss**: Risk factors for BRVO and CRVO include the following (risk factors may differ for each type of occlusion): hypertension, cardiovascular disease, age, diabetes, smoking, obesity, glaucoma, retinal arteriolar abnormalities, and certain ethnic populations (Rogers et al, 2010; Cugati et al 2006; Rehak et al 2008; The Eye Disease Case-control Study Group, 1993 and 1996).

Important Identified Risk: Vascular occlusion events	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 and PL section 3 contain advice for dose adjustment or interruption for arterial occlusion and venous thromboembolism. SmPC section 4.2 contains guidance on assessment of the cardiovascular status and the management and monitoring of the cardiovascular risk factors. SmPC Section 4.4 and PL Section 2 contain advice on monitoring and managing vascular occlusion events. SmPC section 4.8 and PL section 4. Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Table 22: Summary of Important Potential Risk Teratogenicity

Important Potential Risk: Teratogenicity	
Evidence for linking the risk to the medicine	Non-clinical studies
Risk factors and risk groups	Women of childbearing potential
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2 Recommendation for women to avoid becoming pregnant and for men to not father a child in SmPC section 4.6 and PL section 2. Additional risk minimization measures: None
Additional pharmacovigilance activities	None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

None

II.C.2 Other Studies in Post-Authorisation Development Plan

None