Summary of the Risk Management Plan
for
AYVAKYT® (Avapritinib)

Blueprint Medicines (Switzerland) GmbH

Baarerstrasse 8
6300 Zug
Switzerland

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of AYVAKYT is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of AYVAKYT in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic.

Blueprint Medicines (Switzerland) GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of AYVAKYT.

Summary of Risk Management Plan for AYVAKYT (avapritinib)

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

AYVAKYT's product information (PI) and its package leaflet (PL) give essential information to healthcare professionals and patients on how AYVAKYT should be used.

This summary of the RMP for AYVAKYT should be read in the context of all this information.

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

I. The Medicine and What it is Used for

Gastrointestinal Stromal Tumour

- AYVAKYT is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.

Advanced Systemic Mastocytosis

- AYVAKYT is indicated as monotherapy for the treatment of adult patients with advanced systemic mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), and mast cell leukaemia (MCL).

  AYVAKYT is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50×10^9/L.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of AYVAKYT, together with measures to minimise such risks and the proposed studies for learning more about AYVAKYT'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 PI addressed to patients and healthcare professionals;
- 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.

If important information that may affect the safe use of AYVAKYT is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of AYVAKYT 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 AYVAKYT. 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).

List of Important Risks and Missing Information	
Important identified risks	Intracranial haemorrhage Cognitive effects Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers
Important potential risks	Cardiac toxicity, including QT prolongation Embryofoetal toxicity
Missing information	Use in patients with severe hepatic impairment Drug-drug interactions with CYP3A substrates

II.B Summary of Important Risks

Identified Risk: Intracranial Haemorrhage	
Evidence for linking the risk to the medicine	This risk is based on the events of intracranial haemorrhage (subdural haematoma, haemorrhage intracranial, and cerebral haemorrhage) observed in subjects exposed to avapritinib in the clinical development programme, even though the causality evaluation of the events was confounded by alternative aetiologies or other risk factors. The non-clinical data from the avapritinib development programme showed the development of choroid plexus oedema in dogs at subtherapeutic human exposure (≥0.4 times the human exposure at the clinical dose of 300 mg avapritinib) as well as brain haemorrhage in dogs at exposure comparable to the human exposure at the clinical dose of 300 mg avapritinib.

Identified Risk: Intracranial Haemorrhage	
	In addition, intracranial haemorrhage was associated with use of other tyrosine kinase inhibitors (TKIs) such as dasatinib or imatinib (Mustafa Ali et al. 2015), including their use in patients with GIST (Feki et al. 2015; Theodotou et al. 2016). Lastly, a majority of AdvSM patients with intracranial haemorrhage had severe thrombocytopenia, preceding or at the time of the event.
Risk factors and risk groups	Intracranial haemorrhage occurs in 7% of patients with cancer, and subdural haematoma has been estimated to account for 26% of intracranial haemorrhage found at autopsy in this population of patients (Reichman et al. 2012). Intracranial haemorrhage accounts for nearly one half of all cerebrovascular events in cancer patients, but the risk factors vary between types of cancer (Navi et al. 2010). Intracranial haemorrhage is common in haematological malignancies or in the presence of brain metastases. However, brain metastases are extremely rare in GIST (Naoe et al. 2011) and only 16 cases of brain metastases in patients with GIST were reported in the literature until 2014 (Sato et al. 2014). Events of subdural haematoma in patients with GIST treated with imatinib were reported in the literature (Feki et al. 2015; Theodotou et al. 2016) in the absence of other obvious causes such as head trauma, brain metastases, thrombocytopenia or anticoagulation which represent the most common general risk factors for such events, and the suspected cause was imatinib-related platelet dysfunction. It has been estimated that the rate of imatinib-related intracranial haemorrhage in the absence of other obvious causes may be between 1.9 and 5.7% (Theodotou et al. 2016).

Identified Risk: Intracranial Haemorrhage	
	Thrombocytopenia is a known risk factor for internal haemorrhage, including intracranial haemorrhage. In patients with GIST, thrombocytopenia adverse events (AEs) were observed at a low frequency (18 patients; 3.0%). Grade 1 thrombocytopenia was reported in 16 patients, and Grade 2 and Grade 3 in 1 patient each. However, thrombocytopenia AEs were reported in more than a third of the patients with AdvSM (77 patients; 39.9%) and in more than half of these patients the thrombocytopenia AEs were ≥Grade 3 in severity (43 of 77 patients; 56%). Severe thrombocytopenia (platelet count $< 50 \times 10^9$/L) was identified as the primary risk factor for intracranial haemorrhage in AdvSM. Prior to or at the time of the intracranial haemorrhage events, 10 of the 12 patients with AdvSM with intracranial haemorrhage had severe thrombocytopenia with platelet counts below 50×10^9/L, and 2 patients had mild thrombocytopenia (platelet counts between less than lower limit of normal and 75×10^9/L) at the time of the event. As severe thrombocytopenia is a known complication associated with AdvSM, due to bone marrow infiltration by mast cells, this likely explains the higher frequency of intracranial haemorrhage seen in patients with AdvSM compared with patients with GIST treated with avapritinib. In addition to severe thrombocytopenia prior to or at the time of the intracranial haemorrhage, a review of case reports of patients with intracranial haemorrhage events identified several other potential risk factors for such events including use of concomitant anti-platelet or anti-thrombotic therapy any time from the date of first dose of study drug to the date of last dose of study drug + 30 days, inclusive; elevated international normalised ratio prior to the intracranial haemorrhage event; elevated activated partial thromboplastin time prior to the intracranial haemorrhage event; and avapritinib starting dose > 200 mg once daily.

Identified Risk: Intracranial Haemorrhage	
	A multivariate logistic regression model to evaluate the association between intracranial haemorrhage and each of these 5 potential risk factors identified severe thrombocytopenia (platelet counts $< 50 \times 10^9$/L) as the only statistically significant risk factor (p-value: 0.0292) for intracranial haemorrhage in the AdvSM population. Risk mitigation strategies were implemented for all AdvSM patients to minimise the risk for intracranial haemorrhage. These measures included exclusion of patients with a platelet count $< 50 \times 10^9$/L at baseline, monitoring of platelet count at every treatment cycle, detailed guidance on dose modification, and defining the starting dose of avapritinib to be 200 mg once daily. Additionally, to mitigate against a second bleed, protocols were amended such that patients who experienced an intracranial haemorrhage of any toxicity grade permanently discontinued avapritinib treatment. With such risk minimisation measures, the current intracranial haemorrhage incidence is 2.5% in patients with AdvSM who did not have pre-existing severe thrombocytopenia and were treated at a starting dose of 200 mg once daily.
Risk minimisation measures	<u>Routine risk minimisation measures</u> PI sections *Dosage/Administration*, *Warnings and precautions* and *Undesirable effects* Relevant PL sections Recommendation to perform brain imaging by magnetic resonance imaging or computed tomography if the patient experiences clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, or focal weakness) is included in PI section *Warnings and precautions* and relevant PL section. Recommendation to permanently discontinue treatment if intracranial haemorrhage of any grade occurs is included in PI sections *Dosage/Administration* and *Warnings and precautions*.

Identified Risk: Intracranial Haemorrhage	
	Recommendation to interrupt dosing in patients with AdvSM until platelet count is $\geq 50 \times 10^9$/L, then resume at reduced dose, is included in PI section *Dosage/Administration*. Recommendation for platelet support in patients with AdvSM if the platelet count does not recover above 50×10^9/L is included in PI section *Dosage/Administration*. Recommendations for platelet count monitoring in patients with AdvSM are included in PI section *Warnings and precautions*. Recommendation to temporarily stop treatment and contact treating physician if symptoms such as severe headache, vision problems, severe sleepiness, or severe weakness on one side of the body (signs of bleeding in the brain) occur is included in the relevant PL section. Restricted medical prescription <u>Additional risk minimisation measures</u> None

Identified Risk: Intracranial Haemorrhage	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BLU-285-1406 Additionally, the post-authorisation efficacy study BLU-285-1101 will provide further information on the risk. See section II.C of this summary for an overview of the post-authorisation development plan.

Feki J, Marrekchi G, Boudawara T, Rekik N, Maatouq S, Boudawara Z, et al. (2015). "Subdural hematoma during therapy of gastro-intestinal stromal tumor (GIST) with Imatinib mesylate." Gulf J Oncolog 1(17): 92-5.

Mustafa Ali MK, Sabha MM, Al-Rabi KH (2015). "Spontaneous subdural hematoma in a patient with Philadelphia chromosome-positive acute lymphoblastic leukemia with normal platelet count after dasatinib treatment." Platelets 26(5): 491-4

Naoe H, Kaku E, Ido Y, Gushima R, Maki Y, Saito H, et al. (2011). "Brain metastasis from gastrointestinal stromal tumor: a case report and review of the literature." Case Rep Gastrointest Med 5(3): 583-9.

Navi BB, Reichman JS, Berlin D, Reiner AS, Panageas KS, Segal AZ, et al. (2010). "Intracerebral and subarachnoid hemorrhage in patients with cancer." Neurology 74(6): 494-501.

Reichman J, Singer S, Navi B, Reiner A, Panageas K, Gutin PH, et al. (2012). "Subdural hematoma in patients with cancer." Neurosurgery 71(1): 74-9.

Sato K, Tanaka T, Kato N, Ishii T, Terao T, Murayama Y (2014). "Metastatic cerebellar gastrointestinal stromal tumor with obstructive hydrocephalus arising from the small intestine: a case report and review of the literature." Case Rep Oncol Med 2014: 343178.

Theodotou CB, Shah AH, Ivan ME, Komotar RJ (2016). "Subdural hematoma in a patient taking imatinib for GIST: a case report and discussion of risk with other chemotherapeutics." Anticancer Drugs 27(3): 259-63.

Identified Risk: Cognitive Effects	
Evidence for linking the risk to the medicine	This risk is based on the events of cognitive effects (e.g. memory impairment, cognitive disorder, confusional state, amnesia, somnolence, speech disorder, encephalopathy, delirium, mental impairment, hallucination, mood altered, agitation, disorientation, personality change, dementia, mental status change, and psychotic disorder) observed with increased frequency in subjects exposed to avapritinib in the clinical development programme. In addition, cognitive effects have been identified in association with other authorised TKIs such as larotrectinib (Vitrakvi PI, 2019) and lorlatinib (Lorviqua PI, 2019).

Identified Risk: Cognitive Effects	
Risk factors and risk groups	Several risk factors and risk groups prone to develop cognitive effects have been identified based on quantitative and qualitative analysis of available data. These include increased age, medical history of cognitive effects, together with polypharmacy and use of central nervous system medications, increased avapritinib dosage and other concurrent pathologies or disease progression. Analyses of patients in the overall safety population (N=803) showed that the incidence of cognitive effects was slightly higher in patients aged ≥65 years compared with patients aged <65 years (42.4% vs 38.1%). This difference is not unexpected because cognitive issues are known to increase with age (Harada et al. 2013). Furthermore, this is in accordance with other studies that found similar correlation between the age of the patient and development of cognitive effects while undergoing anti-cancer therapy (Ahles et al. 2010). There appeared to be a slightly higher incidence of cognitive effects in female compared to male patients (44.9 vs 37.2%) and in white compared to non-white patients (41.4% vs 36.8%). The incidence of events of cognitive effects was higher in patients from North America compared with patients from Europe or Australia and Asia (51.5% vs 31.2% and 31.9%, respectively). This difference appears to be driven by a higher incidence of events of memory impairment in North American patients compared with patients from the above regions (31.1% vs 10.7% and 14.2%). The cause of this observation is not clear. The incidence of cognitive effects was also found to be higher in patients with prior regorafenib use compared with patients with no regorafenib use in the GIST population. Other variables that did not appear to show a significant impact on the incidence of cognitive effects included prior number of TKI therapies and total duration of prior TKI therapy. A multivariable logistic regression analysis performed for cognitive effects of any grade showed that the odds

Identified Risk: Cognitive Effects	
	of experiencing a cognitive effect were increased by a multiplier of 167% if a patient had medical history of cognitive effects. This is in accordance with publications indicating that the level of cognitive reserve prior to treatment plays a role in development of cognitive effects during anti-cancer therapy (Ahles et al. 2010). This refers to the innate and developed cognitive capacity, which is influenced by various factors, including genetics, education, occupational attainment, and lifestyle. Results of one longitudinal study showed that patients who had lower pre-treatment cognitive reserve performed worse on measures of Processing Speed compared with patients not exposed to chemotherapy and healthy controls (Ahles et al. 2010). As such, patients with higher baseline cognitive performance may have more cushion against cognitive detriments than individuals with a lower baseline cognitive performance.

Identified Risk: Cognitive Effects	
Risk minimisation measures	<u>Routine risk minimisation measures</u> PI sections *Dosage/Administration*, *Warnings and precautions*, *Effects on ability to drive and use machines* and *Undesirable effects* Relevant PL sections Recommendations for dose modification in case of Grade 1-Grade 3 events is included in PI section *Dosage/Administration*. Recommendation to permanently discontinue therapy if Grade 4 cognitive effects occur is included in PI section *Dosage/Administration*. Restricted medical prescription <u>Additional risk minimisation measures</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Study BLU-285-1406 Additionally, the post-authorisation efficacy study BLU-285-1101 will provide further information on the risk. See section II.C of this summary for an overview of the post-authorisation development plan.

Vitrakvi (larotrectinib) Summary of Product Characteristics. Leverkusen, Germany: Bayer AG; 2019. Available from: https://www.ema.europa.eu/en/documents/product-information/vitrakvi-epar-product-information_en.pdf [accessed 11 May 2020].

Lorviqua (lorlatinib) Summary of Product Characteristics. Bruxelles, Belgium: Pfizer Europe MA EEIG; 2019. Available from: https://www.ema.europa.eu/en/documents/product-information/lorviqua-epar-product-information_en.pdf [accessed 11 May 2020].

Harada CN, Natelson Love MC, Triebel KL (2013). "Normal cognitive aging." Clin Geriatr Med 29(4): 737-52.

Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS, et al. (2010). "Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve." J Clin Oncol 28(29): 4434-40.

Identified Risk: Drug-Drug Interactions with Moderate or Strong CYP3A Inhibitors or Inducers	
Evidence for linking the risk to the medicine	The data from the non-clinical studies showed that in vitro, avapritinib is predominantly metabolised by cytochrome P450 (CYP) isozyme 3A (CYP3A), and thus, plasma levels of avapritinib can be affected when administered concomitantly with a moderate or strong CYP3A inhibitor or inducer. The only clinical data available originated from the single-dose, pharmacology Study BLU-285-0104 conducted in healthy volunteers, which showed that plasma exposure of avapritinib was modulated in the presence of the strong CYP isozyme 3A4 (CYP3A4) inducer rifampicin and strong CYP3A4 inhibitor itraconazole. The clinical outcomes of such effects and the overall impact on patients treated with avapritinib remains unknown.
Risk factors and risk groups	No specific risk factors or risk groups have yet been established for avapritinib.
Risk minimisation measures	<u>Routine risk minimisation measures</u> PI sections *Dosage/Administration*, *Warnings and precautions*, *Interactions*, and *Pharmacokinetics* Relevant PL section Concomitant use with strong CYP3A inhibitors must be avoided. Concomitant use with moderate CYP3A inhibitors should be avoided. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib must be reduced from 300 mg orally once daily to 100 mg orally once daily for patients with GIST, and from 200 mg orally once daily to 50 mg orally once daily for patients with AdvSM, as stated in PI section *Dosage/Administration*. Restricted medical prescription <u>Additional risk minimisation measures</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Study BLU-285-1406

Identified Risk: Drug-Drug Interactions with Moderate or Strong CYP3A Inhibitors or Inducers	
	Additionally, the post-authorisation efficacy study BLU-285-1101 will provide further information on the risk. See section II.C of this summary for an overview of the post-authorisation development plan.

Potential Risk: Cardiac Toxicity, Including QT Prolongation	
Evidence for linking the risk to the medicine	The non-clinical studies did not show any effects of avapritinib on the cardiovascular system. In clinical Study BLU-285-1101, a minor increase in corrected QT interval (QTc) was reported at 300/400 mg once daily dose of avapritinib in 3.9% of patients (13/335). The estimated mean change from baseline in QT interval corrected using Fridericia's formula (QTcF) was 6.55 ms (90% confidence interval: 1.80 to 11.29) at the observed steady state geometric mean maximum concentration of 899 ng/mL. These increases were not clinically relevant and no effect on heart rate or cardiac conduction (PR, QRS, and RR intervals) was observed. Cardiac toxicity seen mostly with multitarget TKIs ranged from asymptomatic QT prolongation to reduction in left ventricular ejection fraction, symptomatic congestive heart failure, acute coronary syndromes and myocardial infarction. Hypertension and sudden death have also been associated with treatment with these agents (Chen and Ai 2016; Lee and Kim 2018; Orphanos, 2009). The relevance of these findings to avapritinib remains unknown. The potential for QT prolongation is considered a class effect of small molecule TKIs despite potential differences between individual agents. While dasatinib, vandetanib, sorafenib, nilotinib, or sunitinib showed QT prolongation frequently (>5% of patients), based on the large systematic review of commonly used cancer drugs to determine the incidence of QT prolongation and clinically relevant arrhythmias (Porta-Sanchez et al. 2017), QT prolongation was infrequent or absent with afatinib, crizotinib, ceritinib, dovitinib, imatinib, lapatinib, lenvatinib, nintedanib, pazopanib, and ponatinib.

Potential Risk: Cardiac Toxicity, Including QT Prolongation	
	However, when present, QT prolongation had only rarely clinically relevant consequences, defined as arrhythmias and sudden cardiac death (Porta-Sanchez et al 2017).
Risk factors and risk groups	Patients with a prior history of cardiac disease are in general at higher risk of cardiac damage associated with TKIs (Lee and Kim, 2018). Patients with underlying electrocardiogram or cardiac abnormalities, including patients with a prolonged QTc, defined as QTcF of >480 ms, with a history of prolonged QT syndrome or torsade de pointes or patients with a family history of prolonged QT syndrome may be at higher risk of effects on QT interval and were, therefore, excluded from the clinical trials with avapritinib but are expected in clinical practice within the target population of avapritinib. Concomitant treatment with drugs with a known potential to prolong QT interval such as azole antifungals, fluoroquinolones, macrolides and others may increase the risk. Additionally, elderly patients or patients with electrolyte imbalance are at higher risk of QTc prolongation (Kloth et al. 2015).
Risk minimisation measures	<u>Routine risk minimisation measures</u> PI sections *Warnings and precautions*, *Undesirable effects* and *Properties/Effects* Relevant PL sections Restricted medical prescription <u>Additional risk minimisation measures</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Study BLU-285-1406 Additionally, the post-authorisation efficacy study BLU-285-1101 will provide further information on the risk. See section II.C of this summary for an overview of the post-authorisation development plan.

Potential Risk: Cardiac Toxicity, Including QT Prolongation

Chen ZI, Ai DI (2016). "Cardiotoxicity associated with targeted cancer therapies." Mol Clin Oncol 4(5): 675-81.

Kloth JSL, Pagani A, Verboom MC, Malovini A, Napolitano C, Kruit WHJ, et al. (2015). "Incidence and relevance of QTc-interval prolongation caused by tyrosine kinase inhibitors." Br J Cancer 112(6): 1011-6.

Lee W-S, Kim J (2018). "Cardiotoxicity associated with tyrosine kinase-targeted anticancer therapy." Mol Cell Toxicol 14(3): 247-54.

Orphanos GS, Ioannidis GN, Ardavanis AG (2009). "Cardiotoxicity induced by tyrosine kinase inhibitors." Acta Oncol 48(7): 964-70.

Porta-Sanchez A, Gilbert C, Spears D, Amir E, Chan J, Nanthakumar K, et al. (2017). "Incidence, Diagnosis, and Management of QT Prolongation Induced by Cancer Therapies: A Systematic Review." J Am Heart Assoc 6(12).

Potential Risk: Embryofoetal Toxicity	
Evidence for linking the risk to the medicine	Data from the rodent embryofoetal development studies showed that avapritinib has embryotoxic effects. These results are further supported by the post-marketing data for other TKI agents such as imatinib in pregnant women showing that maternal exposure during the first trimester of pregnancy can lead to foetal development complications and spontaneous abortion (National Toxicology Program 2013, Abruzzese et al. 2014). No data on the use of avapritinib during pregnancy are available.
Risk factors and risk groups	No specific risk factors or risk groups, other than exposure in pregnant women during the first trimester of pregnancy, have yet been identified.
Risk minimisation measures	<u>Routine risk minimisation measures</u> PI sections *Pregnancy, lactation* and *Preclinical data* Relevant PL section Recommendation for female patients of childbearing potential and male patients with female partners of childbearing potential to use effective contraception during treatment and for 1 month after the last dose of avapritinib, is included in PI section *Pregnancy, lactation* and relevant PL section. Restricted medical prescription

Potential Risk: Embryofoetal Toxicity	
	Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BLU-285-1406 Additionally, the post-authorisation efficacy study BLU-285-1101 will provide further information on the risk. See section II.C of this summary for an overview of the post-authorisation development plan.

Abruzzese E, Trawinska MM, Perrotti AP, De Fabritiis P (2014). "Tyrosine kinase inhibitors and pregnancy." J Cereb Blood Flow Metab 6(1): e2014028-e.

National Toxicology Program (2013). "Monograph. Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy." (2): i-214.

Missing Information: Use in Patients with Severe Hepatic Impairment	
Risk minimisation measures	Routine risk minimisation measures PI sections *Dosage/Administration* and *Pharmacokinetics* Restricted medical prescription Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BLU-285-1406 Study BLU-285-0107 Additionally, the post-authorisation efficacy study BLU-285-1101 will provide further information on the missing information. See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Drug-Drug Interactions with CYP3A Substrates	
Risk minimisation measures	Routine risk minimisation measures PI sections *Interactions* and *Pharmacokinetics* Relevant PL section Restricted medical prescription Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BLU-285-1406 Drug-drug Interaction Study Additionally, the post-authorisation efficacy study BLU-285-1101 will provide further information on the missing information. See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies which re Conditions of the Marketing Authorisation

Post-authorisation safety study

Observational safety and efficacy study (Study BLU-285-1406)

Purpose of the study:

To address the specific obligation of the conditional marketing authorisation in Europe and to provide further evidence of the positive benefit-risk profile of avapritinib in patients with metastatic and unresectable GIST harbouring D842V mutations in PDGFRA, an excessively rare disease with high unmet medical need, this study aims to collect additional long-term safety and efficacy data in the first-line population.

The primary objective is a long-term safety of avapritinib while the secondary objective is a long-term efficacy of avapritinib.

Post-authorisation efficacy study

Clinical efficacy and safety study BLU-285-1101

Purpose of the study:

The primary objective of this study is to identify the maximum tolerated dose and assess safety and tolerability and to determine the overall response rate, safety and tolerability of avapritinib in patients with GIST who have a D842V mutation in PDGFRA.

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

A Study to Evaluate the Impact of Severe Hepatic Impairment on Pharmacokinetics of Avapritinib (Study BLU-285-0107)

Purpose of the study:

The primary objective is to characterise the pharmacokinetics of avapritinib in patients with severe hepatic impairment.

Drug-Drug Interaction Study (Study BLU-285-1107)

Purpose of the study:

The primary objective is to investigate the net effect of CYP3A inhibition and induction by avapritinib on midazolam pharmacokinetics in patients.

The effect of avapritinib on the pharmacokinetic parameters of midazolam as well as safety will be assessed.