NOVARTIS

Chief Medical Office & Patient Safety

PZP034 (pazopanib)

PZP034A

EU Safety Risk Management Plan

Active substance (INN or common name):	Pazopanib
Product concerned (brand name):	Votrient®
Document status:	Final
Version number:	17.4
Data lock point for this RMP:	30-Sep-2018 (post-marketing Data lock point) and 31-Jul-2015 (clinical trial Data lock point)
Date of final sign off:	26-Jan-2022

Template Version 6.3, Effective from 24-Feb-2021

Rationale for submitting an updated RMP:

This Risk Management Plan (RMP) for Votrient has been updated to reflect the following changes: (a) Removal of two ongoing clinical studies described under Part III and Part IV; and (b) Revision of ATC code.

Historically, studies CPZP034A2301 (COMPARZ; hereafter referred to as Study A2301) and CPZP034A2201 (COMPARZ substudy; hereafter referred to as Study A2201) were part of a group of postapproval commitments related to the initial marketing authorization for Votrient in the EU: these commitments were completed on 14-Jun-2013 (Commitments SOB001 and SOB002) and 25-Sep-2014 (Commitment ANX-012), respectively. However, these two studies were inadvertently left in the table of ongoing Category 2 studies after their completion and the postmarketing commitments were met. Since these two studies have not been added based on any specific request made since then, and since they do not address any safety concern, they now appear in Table 14-2 "Completed studies" of Annex 2. In addition, the ATC code of pazopanib has been updated for consistency with WHO and the approved SmPC.

The sole purpose of this minor RMP Update is to reflect that described above.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP Version 17.3
Part I	Revision of ATC code.
Part II	No change.
Part III	Removal of 2 clinical studies: Study A2301 and Study A2201 as Category 2 studies: these do not specifically address any safety concern.
Part IV	No change.
Part IV	No change.
Part V	No change.
Part VI	Removal of 2 clinical studies: Study A2301 and Study A2201 as Category 2 studies: these do not specifically address any safety concern.
Part VII	Removal of 2 clinical studies: Study A2301 and Study A2201 as Category 2 studies: these do not specifically address any safety concern.

Other RMP versions under evaluation:

No other versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 17.3

Approved with procedure no.: EMEA/H/C/001141/IB/0066

Date of approval (opinion date): 26-May-2021

QPPV name:

Dr David Lewis

QPPV oversight declaration:

The content of this RMP has been reviewed and approved by the Marketing Authorization Holder's (MAH) QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse event
ALT	Alanine aminotransferase
AS	Advanced angiosarcoma
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCRP	Breast cancer resistance protein
CDP	Clinical development plan
CHF	Congestive heart failure
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
DM	Diabetes mellitus
DVT	Deep vein thrombosis
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GI	Gastrointestinal
HLA	Human leukocyte antigen
HR	Heart rate
HRQoL	Health-related quality of life
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PRES	Posterior reversible encephalopathy syndrome
PSUR	Periodic Safety Update Report
PT	Preferred term
PTY	Patient-treatment-years
RCC	Renal cell carcinoma
RMP	Risk Management Plan
RR	Relative risk
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	System organ class
STS	Soft tissue sarcoma
STY	Subject-treatment-years
TMA	Thrombotic microangiopathy
ULN	Upper limit of normal
VEGFR	Vascular endothelial growth factor receptor

1 Part I: Product Overview

Table 1-1 Part I.1 - Product Overview

Active substance (INN or common name)	Pazopanib
Pharmacotherapeutic group (ATC Code)	L01XE03
Marketing Authorization Holder (MAH)	Originator: GlaxoSmithKline (GSK) Current: Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Votrient
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Multi-target tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and -β, and c-Kit tyrosine kinases.
	Summary of mode of action: In vitro, pazopanib dose-dependently inhibits ligand-induced autophosphorylation of VEGFR-2, c-Kit, and PDGFR-β receptors. In vivo, pazopanib inhibits VEGF-induced VEGFR-2 phosphorylation in mouse lung, angiogenesis in various animal models, and growth of multiple human tumour xenografts in mice.
	Important information about its composition: As pazopanib HCl is not a vaccine or biologic derivate, this is not applicable.
Hyperlink to the Product Information	[Current approved SmPC]
Indications in the EEA	Current: Votrient (pazopanib) is indicated for the treatment of adult patients with: (1) advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease, as first-line; and (2) selective subtypes of advanced soft tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 mo after (neo) adjuvant therapy. Efficacy and safety have only been established in certain STS histological tumor subtypes.
	Proposed: not applicable.
Dosage in the EEA	Current: 800 mg once daily
	Proposed: not applicable.
Pharmaceutical forms and strengths	Current: 200-mg and 400-mg film-coated, pink, capsule-shaped oral tablets (FCT) containing pazopanib HCl at a strength of 200 mg and 400 mg, respectively.
	Proposed: not applicable.
Is the product subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indications and target population

2.1 Indication: RCC

RCC originates in the renal tubule cells and was the most common (85%) of several clinically and epidemiologically distinct types of renal carcinoma (Lipworth et al 2006). The main histologic tumor types included: clear cell (nonpapillary), papillary (chromophilic), chromophobe, oncocytic, collecting duct, and unclassified (Cohen and McGovern 2005).

Incidence:

In the EU, RCC accounted for approximately 3.1% of all cancers in males vs. 2.1% in females (Curado et al 2007).

In the EU, the incidence rate of RCC was higher in males vs. females. Annual incidence rates ranged: 7.9 to 28.7/100000 for males and 3.9 to 18.8/100000 for females (Parkin 2005). Generally, incidence rates observed in Northern Europe were at or below the EU average at 15.4 and 9.4 for males and females, respectively. No consistent patterns of higher / lower vs. average rates were observed in the remaining EU regions: estimated incidence rates varied considerably amongst countries within the other regions.

In the US, RCC was relatively rare with a lifetime risk of 1 in 61 for males and 1 in 103 for females (American Cancer Society 2013). RCC accounted for approximately 3.5% of all cancers diagnosed in the US (Jemal et al 2007). The 2008 annual incidence of RCC was estimated to be 16.2/100000 males and 8.0/100000 females, making it the seventh most common cancer for men and ninth for women at that time (Jemal et al 2007).

At the time of the original submission, GSK projected approximately 59000 new cases annually in the EU and 38000 in the US (Jemal et al 2007).

Table 2-1 Incidence: RCC incidence rates per 100000 persons/year in EU and US by sex during 2008

Country[1]	Incidence	
	Male	Female
EU		
Austria	18.4	12.3
Belgium	13.9	8.0
Bulgaria	7.9	3.9
Cyprus	19.6	10.4
Czech Republic	28.7	18.8
Denmark	15.2	10.1
Estonia	19.3	14.7
Finland	16.9	12.6
France	13.9	8.0
Germany	18.4	12.3
Greece	19.6	10.4

Country[1]	Incidence	
	Male	Female
Hungary	15.1	9.1
Ireland	10.2	5.9
Italy	19.6	10.4
Latvia	14.5	9.7
Lithuania	16.2	9.8
Luxembourg	13.9	8.0
Malta	19.6	10.4
The Netherlands	13.4	8.4
Poland	16.2	9.8
Portugal	8.6	4.4
Romania	15.1	9.1
Slovakia	15.1	9.1
Slovenia	11.9	7.9
Spain	8.6	4.4
Sweden	15.7	11.3
UK	10.2	5.9
US[2]	16.2	8.0

[1] Renal cell carcinoma was defined in CI5-VIII as ICD-10 C64: kidney, excluding renal pelvis. Gender-specific incidence rates for each country were based on a weighted average of all cancer registries in a given country and weights used for each registry were proportional to population size covered by each registry.

[2] Incidence is SEER 17 Regs limited-use, Nov-2006 sub (2000 to 2004), which is linked to county attributes for a total US, 1969 to 2004 counties, released Apr-2007, based on the Nov-2006 submission (SEER unknown).

Source: (Parkin et al 2002, SEER unknown)

Prevalence:

In the US, the 1-year and 5-year prevalence percentages for RCC were 0.00861% and 0.03265%, respectively; the total numbers of prevalent RCC cases were 27863 and 105700 persons, respectively.

Demographics of the population in the RCC authorized indication – age, sex, racial and/or ethnic origin, and risk factors for the disease:

RCC is a disease of older patients: nearly three-quarters are diagnosed between 50 years and 79 years old. Pediatric RCC is rare (0.3% to 1.3% of RCC cases). Of all renal tumors in children, 2% to 6% are RCC (Ötgün et al 2005).

In the US, age-adjusted RCC incidence rates vary slightly by race with higher rates observed in African Americans (Pantuck et al 2001) and increasing in African Americans vs. Whites (Lipworth et al 2006).

The strongest and most well-established risk factor is smoking (Moore et al 2005). Further, it is estimated up to 50% of cases can be attributed to smoking, obesity, and hypertension (Benichou et al 1998, Chiu et al 2006). Other established risk factors are being male (Lipworth

et al 2006, American Cancer Society 2013), older age (Cohen and McGovern 2005, Lipworth et al 2006), dialysis requirement, family history of RCC, and inherited germ-line mutations in high penetrance genes (e.g. VHL, c-MET, TSC1/2) (Moore et al 2005).

The main existing treatment options:

At present, there are 11 targeted drugs approved in Europe or the US for treating advanced RCC: 6 VEGF-receptor tyrosine kinase inhibitors (TKIs) (sorafenib, sunitinib, axitinib, cabozantinib, lenvatinib, pazopanib); 1 monoclonal antibody against VEGF-A (bevacizumab) used in combination with interferon-alpha; 2 mTOR inhibitors (temsirolimus, everolimus); and immunotherapy drugs used either as single-agent or combination therapy (checkpoint inhibitors: nivolumab, ipilimumab).

Based on its favorable benefit-risk, pazopanib is currently recommended by European and US guidelines as a standard first-line therapy for advanced RCC. Pazopanib has been shown to be noninferior to sunitinib in a Phase III clinical study (i.e. GSK VEG108844 and its substudy GSK VEG113078). In addition, pazopanib has demonstrated favorable patient-reported outcomes compared with sunitinib in advanced RCC (Cella and Beaumont 2016). Other drugs (e.g. sunitinib, nivolumab in combination with ipilimumab, cabozantinib, bevacizumab in combination with interferon-alpha, and temsirolimus for poor prognosis risk patients) are also standard therapies in this setting (Powles et al 2017, NCCN 2018a).

Sunitinib and sorafenib are TKIs that inhibit angiogenesis and limit tumor growth. Both were compared against interferon-alpha for efficacy and safety in RCC. Sunitinib, which was approved in the US in 2006 and in the EU in 2007, had a higher overall response rate (46% vs. 12%) and median progression-free survival (PFS) (47.3 w vs. 22 w) in the final analysis (Sutent 2015) and an improved quality of life (Motzer et al 2009). Sorafenib, which was approved in the US in 2005 and in the EU in 2006, had a higher overall response rate (68.2% vs. 39%), similar median PFS (5.7 mo vs. 5.6 mo), and an improved quality of life (Escudier et al 2009). Additionally, in a placebo-controlled study of 903 patients, the median PFS was higher (167 d vs. 84 d) and the median overall survival (OS) was higher (19.3 mo vs. 15.9 mo) in the sorafenib arm vs. the placebo arm (Nexavar 2015). In a randomized Phase II clinical study in metastatic RCC of intermediate or poor risk patients, as an initial therapy cabozantinib (vs. sunitinib) treatment significantly prolonged PFS by independent radiology review committee (IRC), which was the primary endpoint (p=0.0008) (Choueiri et al 2018).

Bevacizumab, a monoclonal antibody against VEGF, was approved in the US in 2004 and in the EU in 2007 in combination with interferon-alpha in the treatment of RCC. When combined with interferon-alpha, vs. interferon-alpha with placebo, bevacizumab showed an improvement in overall response rate (31.4% vs. 12.8%) and PFS (10.2 mo vs. 5.4 mo) but no statistically significant OS benefit (23.3 mo vs. 21.3 mo) (Avastin 2015).

Temsirolimus and everolimus are inhibitors of a protein kinase, which regulates growth factors that stimulate cell growth and angiogenesis, the mammalian target of raptomycin (mTOR). Temsirolimus was approved in the US in 2004 and in the EU in 2007. When compared against interferon-alpha in patients with high-risk RCC, temsirolimus showed an improvement in overall response rate (32.1% vs. 15.5%), OS (10.9 mo vs. 7.3 mo), and PFS (3.8 mo vs 1.9 mo) (Hudes et al 2007). Everolimus, which was approved in the EU and the US in 2009, was

compared against placebo as a second-line therapy in subjects who had mRCC that progressed on prior TKI therapy. Everolimus had a PFS benefit (4.0 mo vs. 1.9 mo) (Motzer et al 2008).

As a combination, in a randomized Phase III clinical study with nivolumab plus ipilimumab or sunitinib, OS (hazard ratio for death, 0.63; $p < 0.001$) and objective response rate (ORR) ($p < 0.001$) were significantly higher among intermediate- and poor-risk patients with previously untreated clear-cell advanced renal-cell carcinoma (Motzer et al 2018).

IL-2 (aldesleukin) is a cytokine that affects the tumor growth through modulation of the immune system and approved in the US in 1992. IL-2 has largely been replaced by newer agents with improved side effect profiles (Escudier 2012); it was designated as an orphan drug in the EU in 2003.

More recently, Cirkel et al (2017) presented efficacy analyses of alternating treatment with pazopanib and everolimus (N=52) compared with continuous pazopanib (N=49) in subjects with clear cell mRCC (i.e. ROPETAR). Efficacy endpoints were survival until first progression or death (primary endpoint, PFS1) and time to second progression or death (secondary endpoint, PFS2). No significant differences in the efficacy parameters were observed. Median PFS1 was 7.4 months (95% confidence interval (CI): 5.6, 18.4) for alternating treatment and 9.4 months (95% CI: 6.6, 11.9) for pazopanib (p=0.37). Median PFS2 was 20.2 months (95% CI: > 10.9) for alternating treatment and 14.5 months (95% CI: > 11.9) for pazopanib (p=0.86). The population in the PFS2 analysis was not likely to be representative of the overall study population: subjects who discontinued the study due to toxicity or death before or at the time of the first progression were excluded. Alternating treatment did not result in improved safety or quality of life (QoL).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Table 2-2 Mortality: RCC cases and deaths in EU and US during 2008

Country/Region	Number of new cases[1,2]	Number of new deaths[1,2,3]
EU	58707	26783
Austria	1283	427
Belgium	1141	542
Bulgaria	443	346
Cyprus	128	44
Czech Republic	2407	1194
Denmark	689	379
Estonia	224	114
Finland	778	380
France	6738	3198
Germany	12614	5217
Greece	1671	456
Hungary	1196	718
Ireland	25	14
Italy	8765	2980
Latvia	270	202

Country/Region	Number of new cases[1,2]	Number of new deaths[1,2,3]
Lithuania	431	267
Luxembourg	52	29
Malta	61	20
The Netherlands	1789	853
Poland	4900	2353
Portugal	686	444
Romania	2565	594
Slovakia	648	246
Slovenia	197	116
Spain	2886	1686
Sweden	1235	659
UK	4886	3307
US	37830	19967

[1] Renal cell carcinoma was defined in CI5-VIII as ICD-10 C64: kidney, excluding renal pelvis. EU projected 2008 cases were calculated by multiplying gender-specific crude incidence rates by the projected mid-year 2008 gender-specific population for each country.
[2] Population estimates were from the United Nations (United Nations unknown).
[3] EU projected 2008 deaths were calculated by multiplying gender-specific crude mortality rates by the projected mid-year 2008 gender-specific population for each country. Morality rates were from the World Health Organization (World Health Organization unknown).
Source: (Parkin et al 2002)

In the EU, mortality rates associated with RCC range from 3.4 to 15.0/100000 for males and 1.7 to 8.6/100000 for females (Parkin 2005). Mortality is generally highest in the Eastern EU countries. At the time of the original submission, GSK projected approximately 27000 RCC-related deaths occurred annually in the EU.

In the US, the mortality rate associated with RCC for males and females is 4.2/100000 (Ries et al 2008). Approximately 20000 RCC-related deaths occurred annually in the US at that time (Jemal et al 2007). Approximately 60% of all RCC cases are diagnosed at the localized stage, usually due to incidental findings with ultrasound, computed tomography scan (CT), or magnetic resonance imaging (MRI) (Pantuck et al 2001). The incidence of advanced stage and unstaged disease, yet, is increasing (Chow et al 2007). The 5-year relative survival for RCC ranges: 96% for in situ cancers to 23% for patients with distant (Stage IV) disease (American Cancer Society 2013). The 5-year survival for all RCC cases combined, independent of stage, was approximately 54% for both males and females (Ries et al 2008). Although low, prognosis for patients diagnosed with RCC has been improving over time. RCC is the tenth most common cancer death among men and the twelfth most common cancer death in women in the US at that time (Jemal et al 2007).

Table 2-3 Mortality: RCC mortality rates per 100000 persons/year in EU and US by sex during 2008

Country	Mortality[1,2]	
	Male	Female
EU		
Austria	5.8	4.4
Belgium	6.7	3.7
Bulgaria	7.6	1.7
Cyprus	6.7	3.5
Czech Republic	15.0	8.6
Denmark	7.6	6.3
Estonia	12.2	5.4
Finland	8.3	6.1
France	6.7	3.7
Germany	7.7	5.0
Greece	5.8	2.4
Hungary	8.7	5.8
Ireland	6.7	2.6
Italy	6.7	3.5
Latvia	10.9	7.2
Lithuania	9.9	6.2
Luxembourg	8.5	3.9
Malta	6.5	3.5
The Netherlands	6.7	3.7
Poland	8.0	4.5
Portugal	3.6	4.7
Romania	3.4	2.2
Slovakia	7.6	1.7
Slovenia	6.7	4.9
Spain	5.2	2.4
Sweden	8.1	6.3
UK	7.0	3.9
US	4.2	4.2

[1] Based on the Nov-2006 SEER data submission that was posted to the SEER website.
[2] Most recent year of data availability was applied. Mortality rates were assumed from neighboring countries for several countries when data were unavailable.
Source: (Ries et al 2008, World Health Organization unknown)

Important comorbidities:

Comorbidities may share a common etiology with RCC or be part of the disease process. However, RCC is primarily a disease of older persons; thus, some of comorbidities may simply be due to older age rather than the disease. Furthermore, cancer cases are often seen by physicians more frequently and are worked up more thoroughly than noncancer controls and therefore, are more likely to have these conditions diagnosed.

As RCC is primarily a disease of elderly patients, comorbidity may significantly affect treatment choices and survival.

GSK's retrospective observational study using the large US medical claims Integrated Healthcare Information Services (IHCIS) database evaluated comorbidities among newly diagnosed RCC. The most prevalent comorbidities included: genitourinary disorders, cardiovascular conditions including hypertension, atrial fibrillation and congestive heart failure (CHF), type II diabetes, anaemia, respiratory diagnoses including chronic obstructive pulmonary disease (COPD), other neoplasms; and less commonly, esophageal reflux, hypothyroidism, and diverticulosis. The five most common comorbidities included: kidney/ureter disorder (47%), unspecified hypertension (37%), abdominal pain (21%), benign hypertension (20%) and unspecified genitourinary disorders (19%). The prevalence of specific comorbidities of interest among 7474 RCC patients followed in this observational study for 6 months following diagnosis are as follows: hypertension (48%), ischaemic heart disease (16.5%), arrhythmia-tachycardia (7.5%), arrhythmia-bradycardia (6.8%), CHF (6.8%), gastrointestinal (GI) bleeding (4.0%), hepatic dysfunction (3.7%), pulmonary thrombosis (3.7%), angina (3.3%), arterial thrombosis (3.1%), myocardial infarction (MI) (1.9%), deep vein thrombosis (DVT) (1.2%), and stroke (0.9%). Results were similar at 3 and 12 months following diagnosis. In contrast, among the cohort of controls who were cancer-free, the prevalence for each of these conditions was statistically-significantly lower: hypertension (23%), ischaemic heart disease (7.5%), arrhythmia-tachycardia (2.6%), arrhythmia-bradycardia (1.6%), congestive heart failure (2.0%), GI bleeding (0.9%), hepatic dysfunction (0.7%), pulmonary thrombosis (0.2%), angina (1.5%), arterial thrombosis (1.1%), MI (0.7%), DVT (0.2%), stroke (0.3%).

GSK's retrospective observational study using the IHCIS database found the most common concomitant medications in RCC patients included: opioid and nonopioid analgesics, proton pump inhibitors, antiemetics, antidepressants, colony stimulating factors, beta blockers, anticoagulants, and nonbarbiturate hypnotics.

Comparable databases with oncology information encompassing countries comprising the EU were not available.

2.2 Indication: STS

STS is a heterogeneous group of more than 50 rare tumors, accounting for less than 1% of all new malignancies in adults and approximately 4% of childhood cancers (Fletcher et al 2002, Altekruse et al 2010). The majority of pediatric STS cases develop as rhabdomyosarcoma (Toro et al 2006); the most common histologic subtypes observed among adults in the US include leiomyosarcoma (20.8%), malignant fibrous histiocytoma (14.9%) and liposarcoma (12.6%) (SEER 2010). Soft tissue, including heart, was the most common site for STS in both adults (48%) and children (53%) (SEER 2010).

Incidence:

The age-adjusted STS incidence rate among adults in the US (7.5/100000) is roughly twice the EU average rate (3.9/100000), resulting in approximately 17451 and 14767, respectively, new adult STS diagnoses estimated to occur in 2011 (Curado et al 2007, SEER 2010, United Nations 2010). EU incidence rates are likely underestimated. In the EU, adult incidence rates were close

to the EU average for most countries. However, incidence rates were much higher in some Central and Eastern countries, attributed predominately to lung sarcomas.

In the US, data are far more complete with regards to capturing sarcomas arising in a more extensive variety of body sites.

Childhood STS incidence rates are similarly low in the US (1.4/100000) and EU (0.88/100000) with only 1146 and 927, respectively, new STS diagnoses predicted to occur among children during 2011 (ACCIS 2010, SEER 2010).

Table 2-4 Incidence: STS incidence rates per 100000 persons/year in EU and US by age group during 2011

Country/Region	Incidence[1]		Number of cases 2011[1,2]	
	Adult	Pediatric	Adult	Pediatric
EU	3.9	0.88	14767	927
		Western EU		
Austria	3.0	0.94[3]	199	16
Belgium	3.3	0.91[3]	275	22
France	4.0	0.91	1898	139
Germany	4.5	0.94	3009	143
Luxembourg	4.0[3]	0.91[3]	15	1
The Netherlands	4.8	1.15	616	45
		Central and Eastern EU		
Bulgaria	3.0	0.69	178	10
Czech Republic	6.2	0.85[3]	518	18
Estonia	3.5	0.69	37	2
Hungary	9.7[3]	0.41[3]	767	8
Latvia	5.2	0.71[3]	93	3
Lithuania	3.8	0.71	97	5
Poland	2.5	0.52	733	42
Romania	3.0[3]	0.41	493	18
Slovak Republic	9.7	0.85	412	10
Slovenia	3.1	0.84	50	3
		Southern EU		
Cyprus	2.1	1.12[3]	14	2
Greece	3.1[3]	1.02[3]	284	22
Italy	3.1	1.02	1529	116
Malta	2.7	1.12	9	1
Portugal	2.5	1.18	212	26
Spain	3.7	0.97	1367	87
		Northern EU		
Denmark	3.8	0.95	156	13
Finland	2.9	1.07	122	13
Ireland	3.5	0.86	119	11
Sweden	2.8	0.99	197	21

Country/Region	Incidence[1]		Number of cases 2011[1,2]	
	Adult	Pediatric	Adult	Pediatric
UK	2.9	0.87	1369	128
US	7.5	1.4	17451	1146

Pediatric defined as younger than 19-year-olds.

Adult defined as 20-year-olds and older.

[1] Gender-specific incidence rates for each country were based on a weighted average of all cancer registries in a given country and weights used for each registry were proportional to population size covered by each registry.

[2] EU incidence rates applied to population estimates provided from World Population Prospects.

[3] Incidence rate data unavailable: rate of neighboring country was applied to estimate the number of 2011 incident cases.

Source: (Curado et al 2007, ACCIS 2010, SEER 2010, United Nations 2010)

Prevalence:

In the EU, there were no published reports or accessible databases on STS prevalence. Applying survival rates (Sant et al 2009, ACCIS 2010) to estimated incident cases, the 5-year prevalence in the EU was approximately 51200 for adults and 3537 for children.

In the US, an estimated 170921 adults and 7515 children were living who at one time were diagnosed with STS (SEER 2010). The 5-year prevalence for adults and children in the US was 52829 and 3728, respectively.

Demographics of the population in the STS authorized indication – age, sex, racial and/or ethnic origin, and risk factors for the disease:

Like many other cancers, STS is a disease of older patients with only approximately 6% of cases occurring in younger patients under 20 years old (SEER 2010). Further, the distribution of specific histologic subtypes is very different for children vs. adults. The vast majority of pediatric STS cases are comprised of rhabdomyosarcoma compared with a wide variety of histologic subtypes that are observed among adults.

In the US, age-adjusted STS incidence rates vary slightly by race, with higher rates observed for African Americans (Toro et al 2006). STS is slightly more common in males (53%) compared with females (47%) in both adults and children.

Several risk factors have been identified in a relatively small number of STS cases, including radiation exposure, occupational exposure to particular chemicals, infection, certain genetic syndromes, and personal history of previous cancers (Spunt et al 2008).

The main existing treatment options:

Surgery and radiotherapy remain the standard initial treatment options for patients with primary resectable adult-type STS; yet, around half of these patients experience recurrence.

Doxorubicin and ifosfamide were the most commonly used drugs for the systemic treatment of STS. In the EU and some other countries outside of the US, Yondelis® (as trabectedin) was approved for patients who progress after receiving doxorubicin and ifosfamide or were unsuited to receive these agents, based on results from a Phase-II randomized clinical study evaluating

two schedules of trabectedin in subjects with leiomyosarcoma and liposarcoma (Demetri et al 2009). Chemotherapies often used in the treatment of STS in the US included doxorubicin, ifosfamide, dacarbazine, gemcitabine and docetaxel. Of these, doxorubicin was the only one with US regulatory approval for a sarcoma indication. For metastatic disease, standard chemotherapy based on anthracyclines (alone or in combination with other agents) is first-line (ESMO 2014, NCCN 2018b). In this setting, the targeted therapy olaratumab (antibody against PDGFR-alpha) was approved for use as combination therapy with doxorubicin (Tap et al 2016).

Limited options are approved as second-line for advanced or metastatic disease, with limited indications for specific STS histologic subtypes, including targeted therapy with pazopanib (for non-adipocytic STS), and chemotherapy with either trabectedin (for liposarcoma and leiomyosarcoma; and translocation-related sarcoma) or eribulin (for liposarcoma). In addition to pazopanib, targeted therapies are only approved for some subtypes, including gastrointestinal stromal tumors (sunitinib and imatinib) (ESMO 2014, NCCN 2018b).

More recently, Kollár et al (2017) presented retrospective efficacy analyses of pazopanib in advanced vascular sarcomas (European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group). The study population (n=52) included subjects with advanced angiosarcoma (AS) (n=40; 76.9%), epithelioid hemangioendothelioma (HE) (n=10; 19.2%), and intimal sarcoma (IS) (n=2; 3.8%) treated in real-world practice at EORTC centers and within the EORTC Phase-II and Phase-III clinical studies. Response rate was 20% (n=8), 20% (n=2), and 100% (n=2) in AS, HE, and IS, respectively. The response rate was similar between cutaneous and noncutaneous AS, and also between radiation-associated and non–radiation-associated AS. Median PFS and median OS from pazopanib initiation was 3 mo (95% CI: 2.1, 4.4) and 9.9 mo (6.5, 11.3) in AS, respectively.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The 5-year survival patterns vary considerably by specific subtype of STS. However, OS with all types combined does not differ substantially by age in the US vs. EU. The 5-year relative survival following STS diagnosis for adults in the US and EU is 63.7% and 59.5%, respectively. Childhood STS survival was similar in the US and EU with 5-year survival proportions of 59.9% and 61%, respectively. Among the EU countries, survival rates in Eastern and Central European countries were considerably lower than the European average.

Important comorbidities:

Little data were available that describe the burden of comorbidities such as cardiovascular disease (CVD), respiratory disease, and diabetes, prior to STS diagnosis or after STS diagnosis and treatment. Less is known about the rate of comorbidities in STS patients related to the cancer itself and its treatment, such as anemia and depression. GSK's retrospective population-based cohort study, (van Herk-Sukel et al 2012) in STS patients assessed the prevalence and incidence of certain comorbidities including CVD, respiratory disease (asthma/COPD), diabetes, anaemia, and depression compared these rates with those observed in a matched noncancer control population.

Patients with STS during 2000 to 2007 (n=533) were selected from PALGA, the Dutch nationwide registry of histo- and cytopathology, and linked to the PHARMO RLS, including

drug use and hospitalizations of approximately 3 million inhabitants in The Netherlands. The occurrences of comorbidities were assessed in the 12 months before and after STS diagnosis.

The prevalence of comorbidities in the 12 months prior to STS diagnosis was assessed. The most prevalent comorbidities in STS patients included: CVD (33%); which was followed by asthma/COPD (10%), diabetes (7%), anaemia (6%), and depression (6%). Incidence rates of the comorbidities were calculated for 3 distinct periods of time after STS diagnosis: 0 to 6 months, 6 to 12 months, and 12-month to end of follow-up time. The IRs of CVD, anemia, and depression were highest during the first 6 months after STS diagnosis (124, 85, and 40/1000 patient-years (PY), respectively), but decreased with increasing amounts of time after STS diagnosis (6 to 12 months: 56, 36, and 5/1000 PY, respectively; 12-month to end of follow-up time: 38, 11, and 13/1000 PY, respectively).

Typical concomitant medications used in the STS patient population were consistent with those patients who have other advanced malignancies and were likely to include, but not restricted to: transfusion of blood and blood products, treatment with antibiotics, antiemetics, antidiarrheal agents, analgesics, erythropoietin, or bisphosphonates.

3 Part II Safety specification Module SII: Nonclinical part of the safety specification

Table 3-1 Key safety findings from nonclinical studies and relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
• **reproductive toxicity:** Drug-related pre- and postimplantation embryolethality and teratogenicity (cardiovascular malformations including retroesophageal right subclavian arteries, missing innominate artery, aortic arch malformations, common truncus) were observed in embryofetal development study in rats. Decreased corpora lutea observed in rats, mice, and monkeys.	Neonate diagnosed with congenital heart disease whose mother was treated with pazopanib during first trimester of pregnancy (Table 5-2). Women of childbearing potential (WOCBP) should be apprised of the potential of fetal harm (in light of embryolethality and teratogenic effects observed in nonclinical studies). Male patients should use adequate male contraception during heterosexual intercourse.
• **developmental toxicity**: Effects on growing or remodeling bones (physeal dysplasia and hypertrophy, trabecular atrophy, periosteal chondroid changes, distortion of digits) and on growing incisor teeth (affecting enamel, dentine layers and pulp) observed in rats.	Potential effect on children's epiphyseal growth plates, nails, and teeth.
• **juvenile animal toxicity**: Mortalities in rat pups dosed with 30, 300, or 1000 mg/kg/day of pazopanib from Day 9 postpartum (pp) were observed. Based on these findings, dosing arms were added in which rats were dosed at 30, 300, and 1000 mg/kg/day beginning Day 21 pp (approximately equal to 2-year-old humans) to Day 35 pp. There was no tolerability issue, excluding reduced body weight gain. Additionally, there were no adverse clinical observations or any drug-related macroscopic necropsy findings observed in these juvenile rats. In a definitive study in juvenile rats with dosing Day 21 pp to Day 62 pp, tibial fractures and adrenal changes limited tolerability at 300 mg/kg/day and were associated with early termination or deaths of some animals. Dilation of duodenal Brunner's gland ducts with glandular atrophy, mucosal erosion and/or inflammation was observed in juvenile rats given pazopanib 300 mg/kg/day. A similar change was previously noted in the duodenum of adult rats dosed at 300 mg/kg/day with pazopanib. The unique aspect of the finding in juvenile rats was the extension of the lesion into the duodenal ampulla of Vater and into the adjacent pancreatic interlobular and extrapancreatic ducts. As no similar histologic change has been noted in other species lacking the VEGFR1 localization, including monkeys dosed up to 1 y, the Brunner's gland change may be rodent specific. Additional changes involved the male reproductive organs at the high dose, which were consistent with decreased testosterone levels and represented delayed sexual maturation associated with the marked decreased body weight gains. The nature of the tolerability issues and potential mechanism of toxicity in preweaning (< 21 d pp) rats was evaluated in an investigative juvenile toxicity study with dosing from Day 9 to	Clinical study NCI ADVL0815 (previously referred to as GSK PZP114411) was amended to increase the lower age limit from > 12 mo to > 2 y (in light of organ growth/maturation effects observed in nonclinical studies). Breast-feeding should be discontinued during pazopanib treatment (Table 5-2).

Key safety findings (from nonclinical studies)	Relevance to human usage
Day 15 pp. Findings suggested that pazopanib markedly interferes with VEGF-dependent glomerular maturation and organ growth/development of kidney, heart, liver, and lung in preweaning rats of this specific age.	
• **nephrotoxicity:** Proteinuria observed in rats, with exacerbation of chronic progressive nephropathy. Renal effects observed in mice at high doses.	Proteinuria reported in subjects.
• **hepatoxicity:** Mild increases in liver enzymes (alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST)) observed in rats. Elevated bilirubin observed in monkeys.	Liver enzyme elevations reported in subjects (Table 8-1). Warnings, precautions, and close monitoring / dosing modifications for drug-induced hepatoxicity.
• **carcinogenicity**: Although pazopanib is not mutagenic, eosinophilic foci and a hepatocellular adenoma observed in the liver of mice in a 13-w toxicity study. In the 2-y nonclinical carcinogenicity studies with pazopanib, increased liver adenomas were observed in mice and duodenal adenocarcinomas in rats.	Findings from the two 2-y carcinogenicity studies were not considered to represent an increased risk for carcinogenicity in humans. The human relevance to these neoplasms is unclear.
Safety pharmacology	
• **cardiovascular system**, including potential effect on the QT interval: In monkeys who received a single IV dose of 3.75 mg/kg pazopanib, mild reversible decreases in heart rate (HR) were observed. No arrhythmias or ECG effects (no QT prolongation) observed when monkeys received single or repeat oral pazopanib dosing for up to 52 w and at doses up to 500 mg/kg/day.	Small effect on QTcF prolongation based on ECG measurements recorded during times of maximal plasma concentrations of pazopanib and its metabolites (previously referred to as GSK VEG111485). Most notable was clinically significant increases in SBP and DBP, and decreases in HR that were observed on Study day 9 in pazopanib-treated subjects and not placebo-treated subjects. There was no clear correlation between the decrease in HR and the magnitude of SBP or DBP elevation relative to baseline. Evaluation of HR data (previously referred to as GSK VEG105192 and GSK VEG110727) revealed occurrences of bradycardia; however, bradycardia was an infrequently reported adverse event (AE).
Other toxicity-related information or data	
• **diarrhea**: Watery diarrhea observed in long-term monkey studies. GI effects observed in mice, rats, and monkeys.	Diarrhea reported in subjects.
• **hematology and bone marrow**: In rats, bone marrow hypocellularity was noted after 4 w of dosing, and decreased red blood cells (RBC) after 26 w of dosing.	Bone marrow hypocellularity and RBC decreases were not specifically reported in the RCC and STS study populations treated with pazopanib. RCC study population: anemia AE reported in 3% pazopanib-treated subjects vs. 8% placebo-treated subjects (GSK VEG105192 (Novartis Study CPZP034A2303: hereafter referred to as Study A2303)). STS study population: postbaseline shifts in hemoglobin to grade-3/4 anemia were observed in laboratory data that were greater in pazopanib-treated subjects vs. placebo-treated subjects (shift to grade 3: 5% vs. < 1%; shift to grade 4: 2% vs. < 1%). However, the percentage of

Key safety findings (from nonclinical studies)	Relevance to human usage
	subjects who had decreases in hemoglobin below normal laboratory ranges was the same in both treatment arms (17%) (GSK VEG110727).

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Votrient was developed by GSK. On 05-May-2015, Novartis became the MAH of Votrient in the EU. Votrient is an established medicinal product (International Birthdate (IBD): 19-Oct-2009). The current efficacy profile remains validated, well-characterized, and stable (PSUR 4).

Cumulatively, approximately 5972 subjects in a GSK- and/or Novartis-sponsored clinical study have been treated/enrolled/randomized to pazopanib, as of 18-Oct-2018 (PSUR 4-Section 5.1).

For purposes of this RMP update, Novartis analyzes data from the 7 clinical studies that previously supported either of the two approved therapeutic indications in fulfillment of current regulatory guidance (Section 1). By indication, they included:

- GSK VEG105192 (Study A2303) (RCC)
- GSK Study VEG102616 (RCC)
- GSK Study VEG107769 (RCC)
- GSK VEG108844 (Novartis Study A2301) (RCC)
- GSK VEG113078 (Novartis Study A2201) (RCC)
- GSK Study VEG110727 (STS)
- GSK Study VEG20002 (STS)

Cumulative clinical trial exposure to subjects within the pazopanib CDP was 1228.4 subject-treatment-years (STY) in the overall population, as of RMP DLP (Table 4-1, Table 4-4). Exposure by therapeutic setting, duration, age-group, sex, race, and known ethnic origin are fully described in Section 4.1.1 and Section 4.1.2.

As pazopanib is administered as 800 mg once daily (Section 1), exposure by dose was not analyzed.

4.1.1 Indication: RCC

Pazopanib exposure was considered adequate within the pazopanib CDP (Table 4-1). Of these, 409 subjects were elderly, i.e. ≥ 65-years-old, and the distribution of elderly subjects did decrease with increasing age. Cumulative pazopanib exposure in this special population was 365.0 STY. By sex, cumulative pazopanib exposure in male subjects was 762.9 STY vs. female subjects at 281.3 STY, which is consistent with the demography of the target population, primarily middle-age and older male patients (Table 4-2, Section 2.1).

Table 4-1 Duration of exposure: RCC, as of RMP DLP 31-Jul-2015 (Safety set)

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG105192)		Comparator-controlled clinical study (VEG108844)	
Duration	Pazopanib N=1140 n (%)	Pazopanib N=290 n (%)	PBO N=145 n (%)	Pazopanib N=554 n (%)	SUN N=548 n (%)
≤ 1 mo	79 (6.9)	18 (6.2)	8 (5.5)	40 (7.2)	73 (13.3)
> 1 mo to ≤ 3 mo	200 (17.5)	49 (16.9)	59 (40.7)	99 (17.9)	76 (13.9)

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG105192)		Comparator-controlled clinical study (VEG108844)	
Duration	Pazopanib N=1140 n (%)	Pazopanib N=290 n (%)	PBO N=145 n (%)	Pazopanib N=554 n (%)	SUN N=548 n (%)
> 3 mo to ≤ 6 mo	207 (18.2)	63 (21.7)	30 (20.7)	99 (17.9)	98 (17.9)
> 6 mo to ≤ 12 mo	276 (24.2)	67 (23.1)	25 (17.2)	145 (26.2)	126 (23.0)
> 12 mo to ≤ 18 mo	132 (11.6)	25 (8.6)	11 (7.6)	75 (13.5)	64 (11.7)
> 18 mo to ≤ 24 mo	88 (7.7)	25 (8.6)	9 (6.2)	33 (6.0)	49 (8.9)
> 24 mo to ≤ 30 mo	80 (7.0)	10 (3.4)	3 (2.1)	40 (7.2)	44 (8.0)
> 30 mo to ≤ 36 mo	41 (3.6)	7 (2.4)	0	15 (2.7)	11 (2.0)
> 36 mo	37 (3.2)	26 (9.0)	0	8 (1.4)	7 (1.3)
STY (y)	**1044.2**	282.5	74.1	465.9	463.3

PBO = placebo; SUN = sunitinib

RCC pooled Safety set includes the following clinical studies: GSK VEG105192 (Study A2303), GSK VEG102616, GSK VEG107769, GSK VEG108844 (Study A2301), GSK VEG113078 (Study A2201).

STY is the sum of each subject's treatment exposure in years.

Source: RMP Version 17.0 attachment to Annex 7-Table 4-1a

Table 4-2 Exposure by sex and age group: RCC, as of RMP DLP 31-Jul-2015 (Safety set)

		Pooled: all clinical studies		Placebo-controlled clinical study (VEG105192)				Comparator-controlled clinical study (VEG108844)			
		Pazopanib N=1140		Pazopanib N=290		PBO N=145		Pazopanib N=554		SUN N=548	
Sex	Age group	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)
Both	Total	1140 (100.0)	1044.2	290 (100.0)	282.5	145 (100.0)	74.1	554 (100.0)	465.9	548 (100.0)	463.3
	< 65 y	731 (64.1)	679.2	196 (67.6)	182.6	85 (58.6)	33.0	341 (61.6)	305.5	329 (60.0)	287.1
	≥ 65 to < 75 y	323 (28.3)	308.5	80 (27.6)	92.4	49 (33.8)	33.3	161 (29.1)	125.5	154 (28.1)	135.2
	≥ 75 to < 85 y	80 (7.0)	55.5	13 (4.5)	7.5	11 (7.6)	7.8	47 (8.5)	33.9	64 (11.7)	41.0
	≥ 85 y	6 (0.5)	1.0	1 (0.3)	0.1	0	NA	5 (0.9)	0.9	1 (0.2)	< 0.1
Male	Total	803 (70.4)	762.9	198 (68.3)	202.6	109 (75.2)	58.7	396 (71.5)	341.5	411 (75.0)	374.1
	< 65 y	537 (47.1)	513.0	134 (46.2)	128.6	68 (46.9)	27.1	256 (46.2)	233.6	254 (46.4)	236.3
	≥ 65 to < 75 y	210 (18.4)	210.6	52 (17.9)	66.7	33 (22.8)	25.4	106 (19.1)	84.0	114 (20.8)	110.3
	≥ 75 to < 85 y	53 (4.6)	38.4	11 (3.8)	7.2	8 (5.5)	6.3	32 (5.8)	23.2	42 (7.7)	27.6
	≥ 85 y	3 (0.3)	0.8	1 (0.3)	0.1	0	NA	2 (0.4)	0.7	1 (0.2)	0.0
Female	Total	337 (29.6)	281.3	92 (31.7)	80.0	36 (24.8)	15.4	158 (28.5)	124.4	137 (25.0)	89.2
	< 65 y	194 (17.0)	166.2	62 (21.4)	54.0	17 (11.7)	5.9	85 (15.3)	71.9	75 (13.7)	50.8
	≥ 65 to < 75 y	113 (9.9)	97.9	28 (9.7)	25.7	16 (11.0)	8.0	55 (9.9)	41.5	40 (7.3)	24.9
	≥ 75 to < 85 y	27 (2.4)	17.0	2 (0.7)	0.3	3 (2.1)	1.5	15 (2.7)	10.7	22 (4.0)	13.5
	≥ 85 y	3 (0.3)	0.2	0	NA	0	NA	3 (0.5)	0.2	0	NA

NA = not applicable

RCC pooled Safety set includes the following clinical studies: GSK VEG105192 (Study A2303), GSK VEG102616, GSK VEG107769, GSK VEG108844 (Study A2301), GSK VEG113078 (Study A2201).

STY is the sum of each subject's treatment exposure in years. STY is based on the number of subjects in each category.

Source: RMP Version 17.0 attachment to Annex 7-Table 4-2a

Table 4-3 Exposure by race/ethnic origin: RCC, as of RMP DLP 31-Jul-2015 (Safety set)

	Pooled: all clinical studies		Placebo-controlled clinical study (VEG105192)				Comparator-controlled clinical study (VEG108844)			
	Pazopanib N=1140		Pazopanib N=290		PBO N=145		Pazopanib N=554		SUN N=548	
Race/ethnic origin	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)
White	834 (73.2)	772.0	250 (86.2)	241.5	122 (84.1)	64.2	347 (62.6)	288.2	355 (64.8)	297.7
Asian	280 (24.6)	254.5	36 (12.4)	38.8	23 (15.9)	9.9	192 (34.7)	167.0	186 (33.9)	160.1
Black or African American	15 (1.3)	7.4	1 (0.3)	1.5	0	NA	10 (1.8)	4.4	5 (0.9)	2.8
Other	10 (0.9)	9.8	3 (1.0)	0.7	0	NA	4 (0.7)	5.8	1 (0.2)	2.2
Missing	1 (0.1)	0.5	0	NA	0	NA	1 (0.2)	0.5	1 (0.2)	0.5

RCC pooled Safety set includes the following clinical studies: GSK VEG105192 (Study A2303), GSK VEG102616, GSK VEG107769, GSK VEG108844 (Study A2301), GSK VEG113078 (Study A2201).

STY is the sum of each subject's treatment exposure in years. STY is based on the number of subjects in each category.

Source: RMP Version 17.0 attachment to Annex 7-Table 4-3a

4.1.2 Indication: STS

Pazopanib exposure was considered adequate within the pazopanib CDP (Table 4-4). Of these, 93 subjects were elderly, i.e. ≥ 65-years-old, and the distribution of elderly subjects did decrease with increasing age. No subject was older than 85-years-old. Cumulative pazopanib exposure in this special population was 34.3 STY. By sex, cumulative pazopanib exposure in male subjects was 73.1 STY vs. female subjects at 111.0 STY. There was no pediatric subject exposed to pazopanib within the pazopanib CDP (Table 4-5), which is consistent with the demography of the target population, primarily middle-age patients (Section 2.2).

Table 4-4 Duration of exposure: STS, as of RMP DLP 31-Jul-2015 (Safety set)

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG110727)	
Duration	Pazopanib N=382 n (%)	Pazopanib N=240 n (%)	PBO N=123 n (%)
≤ 1 mo	55 (14.4)	40 (16.7)	40 (32.5)
> 1 mo to ≤ 3 mo	121 (31.7)	62 (25.8)	48 (39.0)
> 3 mo to ≤ 6 mo	77 (20.2)	50 (20.8)	22 (17.9)
> 6 mo to ≤ 12 mo	87 (22.8)	61 (25.4)	12 (9.8)
> 12 mo to ≤ 18 mo	29 (7.6)	23 (9.6)	0
> 18 mo to ≤ 24 mo	7 (1.8)	4 (1.7)	1 (0.8)
> 24 mo to ≤ 30 mo	3 (0.8)	0	0
> 30 mo to ≤ 36 mo	1 (0.3)	0	0
> 36 mo	2 (0.5)	0	0
STY (y)	**184.2**	111.3	28.2

STS pooled Safety set includes the following clinical studies: GSK VEG110727, GSK VEG20002.
STY is the sum of each subject's treatment exposure in years.
Source: RMP Version 17.0 attachment to Annex 7-Table 4-1b

Table 4-5 Exposure by sex and age group: STS, as of RMP DLP 31-Jul-2015 (Safety set)

		Pooled: all clinical studies		Placebo-controlled clinical study (VEG110727)			
		Pazopanib N=382		Pazopanib N=240 n (%)		PBO N=123 n (%)	
Sex	Age group	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)
Both	Total	382 (100.0)	184.2	240 (100.0)	111.3	123 (100.0)	28.2
	< 18 y	0	NA	0	NA	0	NA
	< 65 y	289 (75.7)	149.9	180 (75.0)	88.4	99 (80.5)	22.3
	≥ 65 to < 75 y	76 (19.9)	28.8	49 (20.4)	19.3	18 (14.6)	3.9
	≥ 75 to < 85 y	17 (4.5)	5.5	11 (4.6)	3.5	6 (4.9)	2.0
	≥ 85 y	0	NA	0	NA	0	NA
Male	Total	168 (44.0)	73.1	97 (40.4)	41.8	54 (43.9)	11.3
	< 65 y	128 (33.5)	59.2	74 (30.8)	33.4	39 (31.7)	7.5
	≥ 65 to < 75 y	31 (8.1)	10.9	18 (7.5)	7.0	11 (8.9)	2.8

		Pooled: all clinical studies		Placebo-controlled clinical study (VEG110727)			
		Pazopanib N=382		Pazopanib N=240 n (%)		PBO N=123 n (%)	
Sex	Age group	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)
	≥ 75 to < 85 y	9 (2.4)	3.1	5 (2.1)	1.3	4 (3.3)	0.9
	≥ 85 y	0	0	0	0	0	0
Female	Total	214 (56.0)	111.0	143 (59.6)	69.5	69 (56.1)	17.0
	< 65 y	161 (42.1)	90.7	106 (44.2)	55.0	60 (48.8)	14.8
	≥ 65 to < 75 y	45 (11.8)	17.9	31 (12.9)	12.3	7 (5.7)	1.1
	≥ 75 to < 85 y	8 (2.1)	2.4	6 (2.5)	2.2	2 (1.6)	1.1
	≥ 85 y	0	NA	0	NA	0	NA

STS pooled Safety set includes the following clinical studies: GSK VEG110727, GSK VEG20002.

STY is the sum of each subject's treatment exposure in years. STY is based on the number of subjects in each category.

Source: RMP Version 17.0 attachment to Annex 7-Table 4-2b

Table 4-6 Exposure by race/ethnic origin: STS, as of RMP DLP 31-Jul-2015 (Safety set)

	Pooled: all clinical studies		Placebo-controlled clinical study (VEG110727)			
	Pazopanib N=382		Pazopanib N=240 n (%)		PBO N=123 n (%)	
Race/ethnic origin	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)	Subjects n (%)	STY (y)
White	169 (44.2)	77.3	169 (70.4)	77.3	91 (74.0)	19.8
Missing[1]	142 (37.2)	72.9	0	NA	0	NA
Asian	57 (14.9)	29.9	57 (23.8)	29.9	27 (22.0)	7.3
Unknown	9 (2.4)	2.8	9 (3.8)	2.8	2 (1.6)	0.3
Black or African American	4 (1.0)	1.1	4 (1.7)	1.1	2 (1.6)	0.2
Other	1 (0.3)	0.1	1 (0.4)	0.1	1 (0.8)	0.6

[1] There were 142 subjects whose race was not collected by GSK as prior MAH during GSK VEG200002.

STS pooled Safety set includes the following clinical studies: GSK VEG110727, GSK VEG20002.

STY is the sum of each subject's treatment exposure in years. STY is based on the number of subjects in each category.

Source: RMP Version 17.0 attachment to Annex 7-Table 4-3b

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

As a well-established medically used medicinal product, Table 5-1 discusses the important exclusion criteria from several pivotal clinical studies across the pazopanib CDP that supported the different therapeutic indications (Table 1-1).

As several special populations were excluded from the pazopanib CDP (Table 5-2), these are not repeated in Table 5-1.

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria[1]	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Subjects with known hypersensitivities to drugs chemically related to pazopanib	Immediate hypersensitivity or delayed reaction to the active substance or any excipient of Votrient FCT (Table 1-1).	No	General awareness using the SmPC stated as contraindications.
Subjects with GI diseases that were specified for the pazopanib CDP	Cases of GI perforation, sometimes fatal, and fistula reported in pazopanib CDP	No	General awareness using the SmPC stated as warnings and precautions for use and as treatment-related ADRs.
Heart failure (NYHA Classes II, III, and IV)	Table 5-2 describes relevant comorbidities in subjects with cardiovascular impairment (cases of cardiac dysfunction)	No	General awareness using the SmPC stated as warnings and precautions for use and as treatment-related ADRs.
QT prolongation	Table 5-2 describes relevant comorbidities in subjects with cardiovascular impairment (cases of cardiac arrhythmias)	No	General awareness using the SmPC stated as warnings and precautions for use and as treatment-related ADRs.
Hypertension	Section 2 describes relevant comorbidities in RCC and STS populations. Pharmacological class effect.	No	General awareness using the SmPC stated as warnings and precautions for use, monitoring and prompt management of blood pressure, and as treatment-related ADRs.
Major surgery (< 28 d)	Cases of skin graft failure and postoperative wound healing reported in pazopanib CDP. Pharmacological class effect.	No	General awareness using the SmPC stated as warnings and precautions for use.
Major hemorrhagic events that were specified for the pazopanib CDP	Cases of hemorrhagic events reported in pazopanib CDP: sometimes fatal.	No	General awareness using the SmPC stated as warnings and precautions for use and treatment-related ADRs.
Hepatic dysfunction	Cases of mild elevated liver enzymes to severe hepatic	No	General awareness using the SmPC stated as warnings and precautions

Criteria[1]	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	failure, sometimes fatal, reported in pazopanib CDP: Table 5-2 describes relevant comorbidities in subjects with hepatic impairment, elderly, population with different relevant, ethnic origin, and subpopulations carrying relevant genetic polymorphisms.		for use and close monitoring for drug-induced hepatotoxicity.
Renal dysfunction	Cases of proteinuria reported in pazopanib CDP: Table 5-2 describes relevant comorbidities in subjects with renal impairment.	No	Missing information only in severe subjects: Less than 4% of an orally administered pazopanib dose is excreted in the urine as pazopanib and metabolites. Results from population pharmacokinetic modelling indicated that renal impairment is unlikely to have clinically relevant effect on pazopanib pharmacokinetics. The current label language is considered sufficient.

NYHA = New York Heart Association; SmPC = Summary of Product Characteristics, package leaflet

[1] Additional criteria that excluded or restricted several special populations within the pazopanib CDP are fully described in Table 5-2 and thus, are not repeated within this summary.

The detailed list of exclusion criteria for the pivotal clinical studies across the pazopanib CDP is summarized in RMP Version 16.1-Table 5 and Table 6.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The pazopanib CDP is unlikely to detect certain types of adverse reactions, such as rare types or with long latency, or those caused by prolonged or cumulative pazopanib exposure.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development program

Table 5-2 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pediatrics	Not included in the pazopanib CDP (Table 4-2, Table 4-5) and very limited exposure. The safety and efficacy of pazopanib in children 2 to 18 y has not been established. Pazopanib should not be used in children younger than 2 y due to safety concerns (Table 3-1). Of relevance, Novartis has a previously agreed-to Paediatric Investigation Plan (PIP) (EMEA-000601-PIP01-09-M04) in 3 conditions (rhabdomyosarcoma, non-rhabdomyosarcoma STS, Ewing's sarcoma family of tumors) that includes a total study population of 56 enrolled subjects (≥ 1 to ≤ 18 year-olds), as of 22-Jan-2019 (GSK VEG116731; Novartis Study PZP034X2203: hereafter referred to as Study X2203). Of these 56, 32 subjects have these conditions.

Type of special population	Exposure
Elderly	Elderly subjects being exposed to pazopanib within the CDP that included 502 ≥ 65-year-olds and 103 ≥ 75-year-olds, as of RMP DLP (Table 4-2, Table 4-5). Of relevance, GSK 200276, a meta-analysis that included 9 GSK Phase II/III clinical studies with pazopanib in the cancer setting (N=2080), indicated increased age (≥ 60 y) was associated with a higher risk of developing ALT > 3 × upper limit of normal (ULN) and up to ALT > 8 × ULN: **ALT thresholds and the elderly within pazopanib CDP, as of RMP DLP** **Threshold** / **Subjects (n)** / **< 60 y N=1126** / **≥ 60 y N=954** ALT > 3 × ULN / 408 / 16% / 24% ALT > 5 × ULN / 234 / 9% / 14% ALT > 8 × ULN / 135 / 5% / 8% (RMP Version 16.1-Section SIV.3, Table 8-1)
Pregnant women	Not included in the pazopanib CDP and very limited exposure. WOCBP should avoid pregnancy during pazopanib treatment. If pazopanib is used during pregnancy and/or a patient becomes pregnant during use, the potential hazard to the fetus should be explained to that pregnant patient (Table 3-1). Twelve (12) pregnancies have been reported in patients who have had pazopanib treatment, as per the most recent assessment (PSUR 4). Of these, 4 were reported as of RMP DLP (RMP Version 16.1-Section SIV.3), 5 cases as of PSUR 3 DLP (PSUR 3-Table 16-33), and 3 cases with exposure during the recent interval assessment (PSUR 4-Section 5.2.2). One (1) out of these 12 cases was considered clinically noteworthy: it was reported in the prior RMP, as detailed: A [redacted]-year-old female patient received pazopanib for thyroid cancer since 16-years-old (i.e. [redacted]-2011). Pazopanib was discontinued [redacted]2014) during her first trimester of pregnancy. About 7 mo after the last pazopanib dose [redacted]-2014), the patient delivered a [redacted] at 38 w gestation. APGAR scores were 8 at 1 min and 9 at 5 min. At an unspecified period after birth, the baby was diagnosed with congenital heart disease characterized by a subaortic septal defect, aortic coarctation, and partial anomalous pulmonary venous return. The baby underwent surgery and was described as "doing well and thriving" postsurgically. The patient resumed pazopanib treatment following birthing for another 5 mo until [redacted]-2015, which was when pazopanib was stopped for an unspecified reason (PSUR 3-Table 16-33).
Breastfeeding women	Not included in the pazopanib CDP and very limited exposure. The safe use of pazopanib during lactation has not been established. Pazopanib should not be used in children younger than 2 y due to safety concerns (Table 5-2). Of relevance (Table 3-1), it is not known whether pazopanib or its metabolites are excreted in human or animal milk. Breastfeeding should be discontinued during pazopanib treatment. Male patients, including those vasectomized, should use condoms during sexual intercourse with pregnant and WOCBP partners for at least 2 w after pazopanib treatment. The risk to a breast-fed child cannot be excluded.
Subjects with relevant comorbidities: • Subjects with hepatic impairment	Subjects with varying degrees (mild, moderate, severe) of hepatic impairment (previously referred to as GSK NCI 8063) were exposed to pazopanib within the CDP, as of RMP DLP. Of relevance, caution and close monitoring (i.e. serum liver function testing (LFT)) is recommended in patients with mild and moderate hepatic impairment. Dose modification (i.e. 200 mg q.d.) is recommended in patients with moderate impairment. Pazopanib is not recommended in patients with severe hepatic impairment (total bilirubin > 3 × ULN regardless of ALT). Actual exposure (both markedly reduced and highly variable) in subjects with severe hepatic impairment was insufficient to obtain a clinically relevant effect.

Type of special population	Exposure
• Subjects with renal impairment	Not included in the pazopanib CDP. Subjects with hemodialysis or peritoneal dialysis were not included in the pazopanib CDP. Caution is recommended in patients with severe renal impairment (creatinine clearance: < 30 mL/min). Of relevance, population pharmacokinetics (PK) modelling indicated impairment is unlikely to have a clinically relevant effect on pazopanib PK. Elimination is slow, pazopanib is excreted primarily in the feces, and the oral dose is renally excreted at a low rate, i.e. < 4% (pazopanib and its metabolites).
• Subjects with cardiovascular impairment	Not included in the pazopanib CDP. The safety and PK of pazopanib in subjects with moderate to severe heart failure or patients with below normal LVEF has not been established (Table 5-1). Of relevance, cardiac dysfunction, e.g. CHF, decreased LVEF, cardiac arrhythmia, QT prolongation, and/or torsades de pointes (TdP) was reported in the pazopanib CDP.
• Immuno-compromised patients	Not included in the pazopanib CDP.
Population with relevant different ethnic origin	Subjects of differing relevant ethnic origin being exposed to pazopanib within the CDP included 337 Asians, as of RMP DLP (Table 4-3, Table 4-6). Of relevance, these subjects included the following Asian countries or regions: Japan, China, Korea, Taiwan, and/or Hong Kong. Data from GSK VEG108844 (Study A2301) and GSK VEG113078 (Study A2201) were pooled by GSK, as detailed in their prospective study design (N=554). Of these, 186 subjects were treated with pazopanib who were categorized as from Asian countries or regions (hereafter referred to as East Asians). Each of these events were addressed among the identified risks in GSK RMP Version 14-SVII.3. Most notably, pooled data indicated East Asians reported increased Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) (PPES), neutropenia, and thrombocytopenia during pazopanib treatment. The most frequently reported AEs in East Asians, primarily grade 1/2, did not result in higher rates of pazopanib treatment discontinuation: **Safety profile of East Asians within pazopanib CDP, as of RMP DLP** **Pooled: GSK VEG108844 (Study A2301) and VEG113078 (Study A2201)**

AE	East Asians N=186		Total N=554	
	Subjects (n)	%	Subjects (n)	%
Hypertension	103	55	257	46
PPES	93	50	163	29
ALT increased	82	44	171	31
AST increased	78	42	148	27
Proteinuria	60	32	98	18
Neutropenia	44	24	62	11
Leukopenia	40	22	51	9
Thrombocytopenia	31	17	57	10
Platelet count decreased	30	16	36	6
Neutrophil count decreased	27	15	28	5
WBC count decreased	24	13	28	5

(RMP Version 16.1-Section SIV.3)

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms: • Subjects with Gilbert's syndrome	DNA collected from 236 subjects treated with pazopanib in the CDP (GSK VEG105192 (Study A2303) and GSK VEG102616) revealed 38 subjects had presence of UGT1A1 gene (TA repeat) polymorphism. Of these, 18 subjects had TA7/TA7 genotype, i.e. predisposition to Gilbert's syndrome. This assessment suggested that pazopanib-induced hyperbilirubinemia may be the result of inhibition of UGT1A1 activity combined with genetic defects in the UGT1A1 gene (Xu et al 2010). GSK VEG117355, a meta-analysis, concluded UGT1A1 polymorphisms were associated with concurrent ALT (≥ 3 × ULN) and bilirubin (≥ 2 × ULN) elevations in subjects treated with pazopanib: this finding may be applied to characterize the risk of liver toxicity. It was observed that a common genetic variant, RS80228453 near the NNT gene, was associated with maximum ALT in subjects treated with pazopanib at a genome-wide significance ($p \leq 0.001$). The human leukocyte antigen (HLA) complex gene HLA-B*57:01 was significantly associated with ALT elevation after adjustment for the number of HLA alleles tested. GSK 201761, a meta-analysis, concluded HLA-B*57:01 allele carriage was significantly associated with time-to-first ALT > 3 × ULN and time-to-first ALT > 5 × ULN. An analysis of these two meta-analyses combined, which included 31 clinical studies with pazopanib, revealed ALT > 5 × ULN occurred in 19% of HLA-B*57:01 allele carriers and in 10% of noncarriers. In this posthoc analysis, 133 subjects, 6%, carried the HLA-B*57:01 allele.

6 Part II Safety specification Module SV: Post-authorization experience

An overview of Votrient exposure in the post-authorization phase containing the same active substance that includes two different methodologies for the current estimation.

6.1 Part II Module SV.1. Post-authorization exposure

The cumulative post-authorization exposure of 87317 patient-treatment-years (PTY) to pazopanib was estimated by combining the GSK data from 19-Oct-2009 to 31-Mar-2015 with the Novartis sales data from 01-Apr-2015 to 30-Sep-2018, i.e. the exposure data cut-off date (DCO) for the most recent calculation (Table 6-1).

The cumulative post-authorization exposure for pazopanib estimated by GSK based on GSK's Intercontinental Medical Statistics (IMS) Health database was 33541 PTY up to 31-Mar-2015 (RMP Version 14-Table 10).

The cumulative post-authorization exposure for pazopanib estimated by Novartis from 01-Apr-2015 to 30-Sep-2018 was 53776 PTY.

The algorithm used to derive post-marketing exposure data is based on the standard 800 mg daily pazopanib dose (Section 6.1.1).

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

The estimated cumulative number of pazopanib tablets sold worldwide to 31-Mar-2015 based on GSK's IMS data was 37684040 (26397591 200-mg tablets and 11286449 400-mg tablets (RMP Version 14-Table 10)) and then, used to estimate the post-marketing exposure by dose (tablet strength) as 1 patient-year = 4 × 200-mg tablets/d for 365 d or 2 × 400-mg tablets/d for 365 d. Thus, the estimated exposure was approximately 33541 PTY.

Novartis estimates of patient exposure based on worldwide sales of active substance sold in kg and the Defined Daily Dose (DDD) of 800 mg.

The sales volume of Votrient from 01-Apr-2015 to 30-Sep-2018 was approximately 15702523.7 kg (15702523630 mg). The algorithm used to derive post-marketing exposure data was based on the DDD. Thus, the estimated exposure was approximately 53776 PTY.

Overall, cumulative post-authorization experience was 87317 PTY, as of 30-Sep-2018.

6.1.2 Part II Module SV.1.2. Exposure

Novartis' calculation of cumulative post-authorization experience, i.e. non-clinical trial exposure, by region is described in Table 6-1.

Table 6-1 Cumulative exposure estimates by region, as of RMP DLP 30-Sep-2018

	Regions (PTY)		
	EEA	**ROW**	**World**
GSK methodology			
19-Oct-2009 to 31-Mar-2015	13397	20144	33541
Novartis methodology			
01-Apr-2015 to 30-Sep-2018	20279	33497	53776
Total	**33676**	**53641**	**87317**

EEA = European Economic Area that includes Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, The Netherlands, United Kingdom. ROW = rest of World

Source: Data on file

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Based on the mechanism of action of pazopanib, a potential for abuse and dependence is not anticipated. The potential for misuse for illegal purposes, e.g. a recreational drug, is considered negligible as Votrient is available by special medical prescription only.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable as the RMP has already been approved (Section 1).

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

There were several risks not considered important for inclusion in the list of safety concerns (EMA 2017) in this RMP update, as detailed in Section 8.2.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

This section is not applicable as the RMP has already been approved (Section 1).

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable as the RMP has already been approved (Section 1).

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There was no change in safety concerns since the last update.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

Novartis acknowledges different methods can be used when presenting aggregate data for the pazopanib important identified and important potential risks.

For full disclosure, presentation by GSK was based on a data-handling rule of on-therapy window as described in the currently-approved pazopanib RMP [Annex 7-Brief statistical description] that included:

- AEs reported from first dose of study treatment to the date of the last dose of study treatment + 28 d

In keeping with GSK's treatment-emergent adverse event (TEAE) definition, Novartis presents these aggregate data from 7 clinical studies (Section 4.1) that previously supported either of the two approved therapeutic indications in fulfillment of current regulatory guidance (EMA 2017).

Finally, Novartis provides the comprehensive listing of all terms, e.g. MedDRA preferred terms (PTs), that contributed to the characterization of each risk. Special care was taken to minimize

the differences in the current risk definition (Annex 7-MedDRA Search terms for spontaneous post-marketing data) vs. GSK's prior terms; however, Novartis remains committed to industry standards, i.e. MedDRA Version 21.1.

The RMP DLP of 31-Jul-2015 was applied to the clinical trial dataset; the RMP DLP of 30-Sep-2018 was applied to post-marketing data.

8.3.1.1 Important identified risks

Important Identified Risk: Hepatic dysfunction

Table 8-1 Clinical trial data of Hepatic dysfunction

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG105192)			Comparator-controlled clinical study (VEG108844)		
RCC Safety set	Pazopanib N=1140 n (%) 95% CI	Pazopanib N=290 n (%) 95% CI	PBO N=145 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI	Pazopanib N=554 n (%) 95% CI	SUN N=548 n (%) 95% CI	Pazopanib vs. SUN: RR 95% CI
Number of subjects with at least one event	417 (36.6) (33.8, 39.5)	88 (30.3) (25.1, 36.0)	13 (9.0) (4.9, 14.8)	3.385 (1.958, 5.850)	252 (45.5) (41.3, 49.7)	242 (44.2) (40.0, 48.4)	1.030 (0.904, 1.174)
Maximum grade							
Grade 3 AEs	147 (12.9)	33 (11.4)	3 (2.1)		92 (16.6)	28 (5.1)	
Grade 4 AEs	27 (2.4)	2 (0.7)	2 (1.4)		21 (3.8)	4 (0.7)	
Grade 5 AEs	3 (0.3)	2 (0.7)	0		0	2 (0.4)	
Serious adverse events (SAEs)	83 (7.3)	10 (3.4)	2 (1.4)		64 (11.6)	23 (4.2)	
AE outcome							
Recovered/resolved	356 (31.2)	70 (24.1)	6 (4.1)		227 (41.0)	203 (37.0)	
Recovering/resolving	23 (2.0)	7 (2.4)	0		8 (1.4)	9 (1.6)	
Not recovered/not resolved	89 (7.8)	18 (6.2)	7 (4.8)		56 (10.1)	50 (9.1)	
Recovered/resolved with sequelae	40 (3.5)	16 (5.5)	0		10 (1.8)	11 (2.0)	
Fatal	3 (0.3)	2 (0.7)	0		0	2 (0.4)	

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG110727)		
STS Safety set	Pazopanib N=382 n (%) 95% CI	Pazopanib N=240 n (%) 95% CI	PBO N=123 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI
Number of subjects with at least one event	24 (6.3) (4.1, 9.2)	17 (7.1) (4.2, 11.1)	2 (1.6) (0.2, 5.8)	NA
Maximum grade				
Grade 3 AEs	6 (1.6)	5 (2.1)	0	
Grade 4 AEs	8 (2.1)	7 (2.9)	1 (0.8)	

RCC Safety set	Pooled: all clinical studies Pazopanib N=1140 n (%) 95% CI	Placebo-controlled clinical study (VEG105192) Pazopanib N=290 n (%) 95% CI	 PBO N=145 n (%) 95% CI	 Pazopanib vs. PBO: RR 95% CI	Comparator-controlled clinical study (VEG108844) Pazopanib N=554 n (%) 95% CI	 SUN N=548 n (%) 95% CI	 Pazopanib vs. SUN: RR 95% CI
Grade 5 AEs	0		0		0		
SAEs	13 (3.4)		13 (5.4)		2 (1.6)		
AE outcome							
Recovered/resolved	9 (2.4)		5 (2.1)		0		
Not recovered/not resolved	3 (0.8)		1 (0.4)		0		
Fatal	1 (0.3)		0		0		

RCC pooled Safety set includes the following clinical studies: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201). STS pooled Safety set includes the following clinical studies: VEG110727, VEG200002.

Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.

NA = Relative risk (RR) is not calculated when at least one of the 2 comparison rates was < 5%.

MedDRA Version 20.1, Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, Case Retrieval Strategy Version 15-Feb-2018.

Source: Attachment to Annex 7 of RMP Version 17.0 Table 8-4a, Table 8-4b

Table 8-2 Important identified risk of Hepatic dysfunction: Other details

Hepatic dysfunction	Details
Potential mechanisms	Unknown. It is known that pazopanib is metabolized in the liver largely through the CYP3A4 pathway and thus, susceptible to DDI that impact this hepatic pathway. Liver injury may be related to production of a toxic intermediate. Furthermore, retrospective meta-analysis or genetic studies (Table 5-2) suggest drugs (simvastatin) or polymorphism (HFE gene) may play a role in serum aminotransferase elevations and Gilbert's syndrome in hyperbilirubinemia, respectively.
Evidence sources and strength of evidence	Supporting data are referenced in the CSRs for the following clinical studies: RCC: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201) STS: VEG110727, VEG200002
Characterization of the risk	Frequency and severity: in the pazopanib CDP, the overall frequency of AEs in pazopanib-treated RCC subjects was 36.6%; the overall frequency of AEs in pazopanib-treated STS subjects was 6.3% (Table 8-1). Of these, most events were manageable and few led to grade-3/4/5. In clinical studies (VEG105192 (Study A2303), VEG102616, VEG107769), events of hepatic dysfunction, such as increased ALT (> 3 × ULN) and increased total bilirubin (TBL) (> 1.5 × ULN) were observed at 18% (95% CI: 14.7, 21.1) and 14% (11.4, 17.3), respectively, in pazopanib-treated RCC subjects (N=586). In the majority of these cases, isolated increased AST and ALT have been reported without concomitant elevation of ALP or bilirubin. Also, in clinical studies (VEG108844 (Study A2301), VEG113078 (Study A2201)), grade-3 or grade-4 increases in hepatic laboratory analyses from

Hepatic dysfunction	Details
	Baseline, such as ALT, AST, TBL, and ALP were 18%, 13%, 3%, and 3%, respectively, in pazopanib-treated RCC subjects (N=547) (RMP Version 16.1-Table 15). Reporting rate of cumulative Hepatic dysfunction post-marketing cases, as of 18-Oct-2018: 41 / 1000 PTY (PSUR 4-Table 16-2). [Excludes subjects in clinical trials and compassionate-use programs.] Reversibility: early recognition of hepatic dysfunction and discontinuation of pazopanib are essential to prevent drug-induced hepatotoxicity.
Risk factors and risk groups	History of alcoholism, nonalcoholic fatty liver disease, viral hepatitis, or hepatic metastases. However, RCC in the absence of hepatic metastases: paraneoplastic syndromes with hepatic-related manifestations, e.g. Stauffer syndrome (Chuang et al 1997). Ages approaching elderly age group: ≥ 60-year-olds (Table 5-2). Known genetic polymorphisms: HLA-B*57:01 allele carrier (Table 5-2). Concomitant use with hepatotoxic drug; concomitant use with simvastatin.
Preventability	Caution, very early detection, and continued monitoring are detailed in the current PI: serum liver tests should be monitored before pazopanib initiation, at Weeks 3, 5, 7, and 9; thereafter, Months 3 and 4; and additional testing as clinically indicated. Periodic testing should continue after Month 4 after pazopanib initiation. Liver function should be monitoring irrespective of age, genotype, or other risk factors / groups.
Impact on the benefit-risk balance of the product	Considering the current benefits (Table 1-1), these data continue to support the favorable benefit-risk balance of pazopanib.
Public health impact	Events are manageable and thus, public health impact considered low.

Important Identified Risk: Cardiac arrhythmias

Table 8-3 Clinical trial data of Cardiac arrhythmias

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG105192)			Comparator-controlled clinical study (VEG108844)		
RCC Safety set	Pazopanib N=1140 n (%) 95% CI	Pazopanib N=290 n (%) 95% CI	PBO N=145 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI	Pazopanib N=554 n (%) 95% CI	SUN N=548 n (%) 95% CI	Pazopanib vs. SUN: RR 95% CI
Number of subjects with at least one event	54 (4.7) (3.6, 6.1)	15 (5.2) (2.9, 8.4)	5 (3.4) (1.1, 7.9)	NA	21 (3.8) (2.4, 5.7)	27 (4.9) (3.3, 7.1)	NA
Maximum grade							
Grade 3 AEs	8 (0.7)	1 (0.3)	1 (0.7)		3 (0.5)	2 (0.4)	
Grade 4 AEs	2 (0.2)	1 (0.3)	0		0	1 (0.2)	
Grade 5 AEs	1 (0.1)	0	1 (0.7)		0	1 (0.2)	
SAEs	9 (0.8)	3 (1.0)	1 (0.7)		2 (0.4)	3 (0.5)	
AE outcome							
Recovered/ resolved	34 (3.0)	8 (2.8)	2 (1.4)		13 (2.3)	16 (2.9)	

Recovering/ resolving	0	0	0	0	1 (0.2)	
Not recovered/ not resolved	19 (1.7)	7 (2.4)	2 (1.4)	7 (1.3)	9 (1.6)	
Recovered/ resolved with sequelae	5 (0.4)	3 (1.0)	0	1 (0.2)	0	
Fatal	1 (0.1)	0	1 (0.7)	0	1 (0.2)	

	Pooled: all clinical studies	**Placebo-controlled clinical study (VEG110727)**		
STS Safety set	**Pazopanib N=382 n (%) 95% CI**	**Pazopanib N=240 n (%) 95% CI**	**PBO N=123 n (%) 95% CI**	**Pazopanib vs. PBO: RR 95% CI**
Number of subjects with at least one event	24 (6.3) (4.1, 9.2)	15 (6.3) (3.5, 10.1)	8 (6.5) (2.8, 12.4)	0.961 (0.419, 2.204)
Maximum grade				
Grade 3 AEs	3 (0.8)	3 (1.3)	1 (0.8)	
Grade 4 AEs	0	0	0	
Grade 5 AEs	1 (0.3)	1 (0.4)	0	
SAEs	1 (0.3)	1 (0.4)	2 (1.6)	
AE outcome				
Recovered/resolved	20 (5.2)	11 (4.6)	6 (4.9)	
Not recovered/not resolved	4 (1.0)	4 (1.7)	2 (1.6)	
Recovered/resolved with sequelae	2 (0.5)	2 (0.8)	0	
Fatal	1 (0.3)	1 (0.4)	0	

RCC pooled Safety set includes the following clinical studies: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201). STS pooled Safety set includes the following clinical studies: VEG110727, VEG200002.

Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.

NA = RR is not calculated when at least 1 of the 2 comparison rates was < 5%.

MedDRA Version 20.1, CTCAE Version 3.0, Case Retrieval Strategy Version 15-Feb-2018.

Source: Attachment to Annex 7 of RMP Version 17.0 Table 8-4a, Table 8-4b

Table 8-4 Important identified risk of Cardiac arrhythmias: Other details

Cardiac arrhythmias	**Details**
Potential mechanisms	Unknown. TKIs can induce electrophysiological abnormalities directly, i.e. block of ion channels, or indirectly, i.e. altered intracellular signaling leading to decreased potassium current, which can then prolong the QT interval and increase the risk for arrhythmia (Shim et al 2017).
Evidence sources and strength of evidence	Supporting data are referenced in the CSRs for the following clinical studies: RCC: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201) STS: VEG110727, VEG200002

Cardiac arrhythmias	Details
Characterization of the risk:	Frequency and severity: in the pazopanib CDP, the overall frequency of AEs in pazopanib-treated RCC subjects was 4.7%; the overall frequency of AEs in pazopanib-treated STS subjects was 6.3%. Cardiac arrhythmias (e.g. palpitations, bradycardia, tachycardia, atrial fibrillation, supraventricular extrasystoles) may be asymptomatic with pazopanib; however, sometimes with fatal outcome (e.g. grade-5 cardio-respiratory arrest, sudden death) in pazopanib CDP (Table 8-3). Of relevance, electrocardiogram QT prolonged events were reported within the pazopanib CDP (Attachment to Annex 7 of RMP Version 17.0 Table 8-4.1a). Reporting rate of cumulative Cardiac arrhythmias post-marketing cases, as of 18-Oct-2018: 3.2 / 1000 PTY (PSUR 4-Table 16-7). [Excludes subjects in clinical studies and compassionate-use programs.]
Risk factors and risk groups	Long QT syndrome (LQTS) or relevant pre-existing cardiac disease. History of QT prolongation. Obesity, hypertension, smoking, dyslipidemia, or in elderly (> 65-year-olds) patients; any other factors/groups associated with ischemic cardiac disease. Electrolyte disturbances of magnesium, potassium, or calcium. Drug or agent known to increase risk of cardiac arrhythmia, e.g. anthracyclines, thoracic radiation therapy. Drug known to prolong the QT interval, e.g. antiarrhythmics.
Preventability	Electrolytes (e.g. calcium, magnesium, potassium) and ECGs should be monitored before pazopanib initiation, and periodically thereafter. Review patient history and strict adherence to risk factors and risk groups guidance, e.g. pazopanib should be used with caution in patients with a history of QT interval prolongation. TdP is listed as an ADR being reported at < 1% of treated patients in the Votrient SmPC.
Impact on the benefit-risk balance of the product	Considering the current benefits (Table 1-1), these data continue to support the favorable benefit-risk balance of pazopanib.
Public health impact	Public health impact considered low.

Important Identified Risk: Hypertension

Table 8-5 Clinical trial data of Hypertension

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG105192)			Comparator-controlled clinical study (VEG108844)		
RCC Safety set	Pazopanib N=1140 n (%) 95% CI	Pazopanib N=290 n (%) 95% CI	PBO N=145 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI	Pazopanib N=554 n (%) 95% CI	SUN N=548 n (%) 95% CI	Pazopanib vs. SUN: RR 95% CI
Number of subjects with at least one event	503 (44.1) (41.2, 47.1)	116 (40.0) (34.3, 45.9)	15 (10.3) (5.9, 16.5)	3.867 (2.346, 6.372)	260 (46.9) (42.7, 51.2)	222 (40.5) (36.4, 44.8)	1.158 (1.013, 1.325)
Maximum grade							
Grade 3 AEs	118 (10.4)	13 (4.5)	1 (0.7)		81 (14.6)	80 (14.6)	
Grade 4 AEs	3 (0.3)	1 (0.3)	0		2 (0.4)	1 (0.2)	

RCC Safety set	Pooled: all clinical studies	Placebo-controlled clinical study (VEG105192)			Comparator-controlled clinical study (VEG108844)		
	Pazopanib N=1140 n (%) 95% CI	Pazopanib N=290 n (%) 95% CI	PBO N=145 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI	Pazopanib N=554 n (%) 95% CI	SUN N=548 n (%) 95% CI	Pazopanib vs. SUN: RR 95% CI
Grade 5 AEs	0	0	0		0	0	
SAEs	14 (1.2)	3 (1.0)	1 (0.7)		8 (1.4)	7 (1.3)	
AE outcome							
Recovered/resolved	295 (25.9)	77 (26.6)	11 (7.6)		142 (25.6)	130 (23.7)	
Recovering/resolving	36 (3.2)	12 (4.1)	1 (0.7)		12 (2.2)	11 (2.0)	
Not recovered/not resolved	178 (15.6)	30 (10.3)	3 (2.1)		110 (19.9)	95 (17.3)	
Recovered/resolved with sequelae	30 (2.6)	2 (0.7)	2 (1.4)		10 (1.8)	8 (1.5)	

STS Safety set	Pooled: all clinical studies	Placebo-controlled clinical study (VEG110727)		
	Pazopanib N=382 n (%) 95% CI	Pazopanib N=240 n (%) 95% CI	PBO N=123 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI
Number of subjects with at least one event	161 (42.1) (37.1, 47.3)	101 (42.1) (35.8, 48.6)	7 (5.7) (2.3, 11.4)	7.395 (3.547 ,15.415)
Maximum grade				
Grade 3 AEs	26 (6.8)	16 (6.7)	0	
Grade 4 AEs	0	0	0	
Grade 5 AEs	0	0	0	
SAEs	3 (0.8)	0	0	
AE outcome				
Recovered/resolved	120 (31.4)	74 (30.8)	4 (3.3)	
Recovering/resolving	2 (0.5)	2 (0.8)	0	
Not recovered/not resolved	50 (13.1)	26 (10.8)	3 (2.4)	
Recovered/resolved with sequelae	5 (1.3)	5 (2.1)	0	

RCC pooled Safety set includes the following clinical studies: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201). STS pooled Safety set includes the following clinical studies: VEG110727, VEG200002.

Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.

NA = RR is not calculated when at least one of the 2 comparison rates was < 5%.

MedDRA Version 20.1, CTCAE Version 3.0, Case Retrieval Strategy Version 15-Feb-2018.

Source: Attachment to Annex 7 of RMP Version 17.0 Table 8-4a, Table 8-4b

Table 8-6 Important identified risk of Hypertension: Other details

Hypertension	Details
Potential mechanisms	Potential mechanism includes blockade of the nitrous-oxide signaling cascade at the phosphatidylinositol 3-kinase and mitogen-activated protein-kinase level. The decrease in production of these vasodilators would result in increased vascular resistance and increased blood pressure (Qi et al 2013). Another postulation includes increased activation of the endothelin-1 system, i.e. potent vasoconstrictor (Hamnvik et al 2015).
Evidence sources and strength of evidence	Supporting data are referenced in the CSRs for the following clinical studies: RCC: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201) STS: VEG110727, VEG200002 Evidence: pooled meta-analysis on pazopanib 800 mg/day of 13 clinical studies in cancer patients (N=1651): overall incidence of hypertension, all grades, 35.9% (95% CI: 31.5, 40.6), grade 3/4, 6.5% (5.2, 8.0); overall risk of hypertension, all grades, RR=4.97 (3.38, 7.30; p < 0.001), grade 3/4, 2.87 (1.16, 7.12; p=0.023). No statistical difference between RCC vs. non-RCC (all grades, RR=1.21; 95% CI: 0.96, 1.53; p=0.11 // grade 3/4, 1.29; 0.80, 2.07; p=0.30) (Qi et al 2013).
Characterization of the risk:	Frequency and severity: in the pazopanib CDP, the overall frequency of AEs in pazopanib-treated RCC subjects was 44.1%; the overall frequency of AEs in pazopanib-treated STS subjects was 42.1%. Mostly nonserious cases (grade-1/2 hypertensive crisis, hypertension); however, cases of new onset of diagnosed elevated BP (systolic BP ≥ 150 mm Hg or diastolic BP ≥ 100 mm Hg) and hypertensive crisis (Table 8-5). Hypertension onset: by Day 9 (38.6% in 3 RCC clinical studies), on Day 9 (40% in 1 STS clinical study), or on or before 17 d (41% in 2 RCC clinical studies) of pazopanib initiation within pazopanib CDP (RMP Version 16.1-Table 15). Reporting rate of cumulative Hypertension post-marketing cases, as of 18-Oct-2018: 24.6 / 1000 PTY (PSUR 4-Table 16-11). [Excludes subjects in clinical trials and compassionate-use programs.] Reversibility: with dose modification and antihypertensive therapy.
Risk factors and risk groups	Hyperlipidemia, obesity and/or DM, smoking, and alcoholism. Patients with significant reductions in LVEF or at risk of cardiac dysfunction (Table 8-9). History of or preexisting hypertension.
Preventability	Blood pressure should be well-controlled prior to pazopanib treatment. Closely monitor for hypertension soon after pazopanib initiation early (< 1 w) and frequently thereafter, to ensure blood pressure management. Blood pressure can be controlled using pazopanib dose modification, e.g. interruption and reinitiation at a reduced dose based on clinical judgement, and concomitant antihypertensive. Permanent discontinuation if evidence of hypertensive crisis or if severe hypertension regardless of pazopanib dose reduction and antihypertensive therapy.
Impact on the benefit-risk balance of the product	Considering the current benefits (Table 1-1), these data continue to support the favorable benefit-risk balance of pazopanib.

Hypertension	Details
Public health impact	Events are manageable and thus, public health impact considered moderate.

Important Identified Risk: Hypothyroidism

Table 8-7 Clinical trial data of Hypothyroidism

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG105192)			Comparator-controlled clinical study (VEG108844)		
RCC Safety set/	Pazopanib N=1140 n (%) 95% CI	Pazopanib N=290 n (%) 95% CI	PBO N=145 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI	Pazopanib N=554 n (%) 95% CI	SUN N=548 n (%) 95% CI	Pazopanib vs. SUN: RR 95% CI
Number of subjects with at least one event	136 (11.9) (10.1, 14.0)	28 (9.7) (6.5, 13.7)	0	NA	96 (17.3) (14.3, 20.7)	184 (33.6) (29.6, 37.7)	0.516 (0.416, 0.641)
Maximum grade							
Grade 3 AEs	0	0	0		0	2 (0.4)	
Grade 4 AEs	0	0	0		0	0	
Grade 5 AEs	0	0	0		0	0	
SAEs	0	0	0		0	0	
AE outcome							
Recovered/resolved	53 (4.6)	11 (3.8)	0		39 (7.0)	86 (15.7)	
Recovering/resolving	9 (0.8)	2 (0.7)	0		4 (0.7)	8 (1.5)	
Not recovered/not resolved	79 (6.9)	16 (5.5)	0		57 (10.3)	113 (20.6)	
Recovered/resolved with sequelae	3 (0.3)	0	0		3 (0.5)	0	

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG110727)		
STS Safety set	Pazopanib N=382 n (%) 95% CI	Pazopanib N=240 n (%) 95% CI	PBO N=123 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI
Number of subjects with at least one event	20 (5.2) (3.2, 8.0)	19 (7.9) (4.8, 12.1)	0	NA
Maximum grade				
Grade 3 AEs	0	0	0	
Grade 4 AEs	0	0	0	
Grade 5 AEs	0	0	0	
SAEs	0	0	0	
AE outcome				
Recovered/resolved	10 (2.6)	10 (4.2)	0	
Recovering/resolving	1 (0.3)	1 (0.4)	0	

Not recovered/not resolved	10 (2.6)	9 (3.8)	0	

RCC pooled Safety set includes the following clinical studies: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201). STS pooled Safety set includes the following clinical studies: VEG110727, VEG200002.
Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.
NA = RR is not calculated when at least one of the 2 comparison rates was < 5%.
MedDRA Version 20.1, CTCAE Version 3.0, Case Retrieval Strategy Version 15-Feb-2018.
Source: Attachment to Annex 7 of RMP Version 17.0 Table 8-4a, Table 8-4b

Table 8-8 Important identified risk Hypothyroidism: Other details

Hypothyroidism	Details
Potential mechanisms	Mechanism of TKI-induced thyroid dysfunction includes transient thyrotoxicosis before developing hypothyroidism suggesting destructive thyroiditis, thyroid radioiodine uptake inhibition, impairment of peroxidase activity, regression of the thyroid vascular bed, or inhibition of the MCT8-specific thyroid hormone cell-membrane transporter (Fallahi et al 2014).
Evidence sources and strength of evidence	Supporting data are referenced in the CSRs for the following clinical studies: RCC: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201) STS: VEG110727, VEG200002
Characterization of the risk:	Frequency and severity: in the pazopanib CDP, the overall frequency of AEs in pazopanib-treated RCC subjects was 11.9%; the overall frequency of AEs in pazopanib-treated STS subjects was 5.2%. Laboratory data analyses revealed thyroid-stimulating hormone (TSH) elevation with T4 suppression in some pazopanib-treated subjects in both the RCC and STS settings (RMP Version 16.1-Table 15). Events of blood TSH increased and confirmed hypothyroidism only in the RCC setting; grade-1/2 hypothyroidism only in the STS setting (Table 8-7). Reporting rate of cumulative Hypothyroidism post-marketing cases, as of 18-Oct-2018: 5.0 / 1000 PTY (PSUR 4-Table 16-12). [Excludes subjects in clinical trials and compassionate-use programs.] Reversibility: hypothyroidism may be asymptomatic; however, medication therapy may be required based on laboratory test results.
Risk factors and risk groups	Prior history of thyroid dysfunction.
Preventability	Thyroid function tests should be performed before pazopanib initiation, and periodically thereafter. Closely monitor for signs and symptoms of thyroid dysfunction. Treatment should be standard medical practice.
Impact on the benefit-risk balance of the product	Considering the current benefits (Table 1-1), these data continue to support the favorable benefit-risk balance of pazopanib.
Public health impact	Events are manageable and thus, public health impact considered low.

Important Identified Risk: Cardiac dysfunction

Table 8-9 Clinical trial data of Cardiac dysfunction

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG105192)			Comparator-controlled clinical study (VEG108844)		
RCC Safety set	Pazopanib N=1140 n (%) 95% CI	Pazopanib N=290 n (%) 95% CI	PBO N=145 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI	Pazopanib N=554 n (%) 95% CI	SUN N=548 n (%) 95% CI	Pazopanib vs. SUN: RR 95% CI
Number of subjects with at least one event	31 (2.7) (1.9, 3.8)	2 (0.7) (0.1, 2.5)	0	NA	27 (4.9) (3.2, 7.0)	23 (4.2) (2.7, 6.2)	NA
Maximum grade							
Grade 3 AEs	6 (0.5)	1 (0.3)	0		5 (0.9)	8 (1.5)	
Grade 4 AEs	1 (0.1)	0	0		0	0	
Grade 5 AEs	2 (0.2)	1 (0.3)	0		1 (0.2)	1 (0.2)	
SAEs	6 (0.5)	1 (0.3)	0		4 (0.7)	5 (0.9)	
AE outcome							
Recovered/resolved	17 (1.5)	1 (0.3)	0		14 (2.5)	13 (2.4)	
Recovering/resolving	2 (0.2)	0	0		2 (0.4)	0	
Not recovered/not resolved	10 (0.9)	0	0		10 (1.8)	9 (1.6)	
Recovered/resolved with sequelae	1 (0.1)	0	0		1 (0.2)	3 (0.5)	
Fatal	2 (0.2)	1 (0.3)	0		1 (0.2)	1 (0.2)	

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG110727)		
STS Safety set	Pazopanib N=382 n (%) 95% CI	Pazopanib N=240 n (%) 95% CI	PBO N=123 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI
Number of subjects with at least one event	21 (5.5) (3.4, 8.3)	21 (8.8) (5.5, 13.1)	5 (4.1) (1.3, 9.2)	NA
Maximum grade				
Grade 3 AEs	3 (0.8)	3 (1.3)	0	
Grade 4 AEs	1 (0.3)	1 (0.4)	0	
Grade 5 AEs	0	0	0	
SAEs	5 (1.3)	5 (2.1)	0	
AE outcome				
Recovered/resolved	8 (2.1)	8 (3.3)	2 (1.6)	
Recovering/resolving	1 (0.3)	1 (0.4)	0	
Not recovered/not resolved	12 (3.1)	12 (5.0)	3 (2.4)	

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG110727)		
STS Safety set	Pazopanib N=382 n (%) 95% CI	Pazopanib N=240 n (%) 95% CI	PBO N=123 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI
Recovered/resolved with sequelae	1 (0.3)	1 (0.4)	0	
Unknown	1 (0.3)	1 (0.4)	0	

RCC pooled Safety set includes the following clinical studies: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201). STS pooled Safety set includes the following clinical studies: VEG110727, VEG200002.

Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.

NA = RR is not calculated when at least one of the 2 comparison rates was < 5%.

MedDRA Version 20.1, CTCAE Version 3.0, Case Retrieval Strategy Version 15-Feb-2018.

Source: Attachment to Annex 7 of RMP Version 17.0 Table 8-4a, Table 8-4b

Table 8-10 Important identified risk of Cardiac dysfunction: Other details

Cardiac dysfunction	Details
Potential mechanisms	A potential mechanism of cardiac dysfunction due to pazopanib is not known. It is possible that patients with a previously damaged myocardium are at greater risk for cardiac dysfunction due to the effect of pazopanib to raise blood pressure and increase afterload via the effects on nitric oxide synthetase (Table 8-6). Different hypotheses of cardiotoxicity mechanism indicate that many of the pathways responsible for proliferation in malignant cells also play important roles in cardiomyocytes as: (a) survival signaling (e.g. sorafenib inhibition of RAF-1 may block survival signaling through the protein-kinase ERK concurrently disinhibiting proapoptotic kinases: this dual action of prosurvival signaling inhibition and apoptotic signaling activation can culminate during cell death); (b) mitochondrial and sarcoplasmic reticulum homeostasis (e.g. sunitinib has been reported to cause ATP depletion in cardiomyocytes through an off-target effect involving AMP-activated protein kinase; and (c) electrical and contractile function (direct or indirect modulation of cardiac ionic currents, resulting in proarrhythmic electrical activity; or, structural remodeling leading to altered myocyte contraction) (Je et al 2009).
Evidence sources and strength of evidence	Supporting data are referenced in the CSRs for the following clinical studies: RCC: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201) STS: VEG110727, VEG200002
Characterization of the risk:	Frequency and severity: in the pazopanib CDP, the overall frequency of AEs in pazopanib-treated RCC subjects was 2.7%; the overall frequency of AEs in pazopanib-treated STS subjects was 5.5%. Ejection fraction decreased can by asymptomatic. Cases of cardiac failure/acute and congestive cardiac failure, left ventricular dysfunction, decreased ejection fraction, cardiomegaly, pulmonary edema, and stress cardiomyopathy may be manageable (e.g. dose interrupted/delayed/reduced); however, major events can be life-threatening (grade-4 stress cardiomyopathy, left ventricular dysfunction) or even fatal (e.g. grade-5 cardiac failure, cardiopulmonary failure) (Table 8-9). Subpopulation: STS subjects within the pazopanib CDP often received prior anthracycline and/or thoracic radiation therapies. GSK as prior MAH decided to amend their relevant protocol to include LVEF monitoring (ECHO or MUGA)

Cardiac dysfunction	Details
	as prior treatment with anthracyclines or chest radiotherapy may increase the risk of cardiac and/or myocardial dysfunction (RMP Version 16.1-Table 15). The cardiotoxicity of the anthracycline class of chemotherapeutic agents is well documented (Pai and Nahata 2000). Out of the 31 (2.7%) of the RCC subjects who had an AE of cardiac dysfunction, 12 subjects also had documented decrease in LVEF with postbaseline and follow-up measurements. 6 out of these 12 subjects also had concurrent hypertension. Similarly, out of the 21 (5.5%) STS subjects who had AE of cardiac dysfunction, 12 subjects also had documented decrease in LVEF with postbaseline and follow-up measurements. 10 out of these 12 subjects also had concurrent hypertension. Hypertension may have exacerbated cardiac dysfunction, especially in subjects at increased risk, such as those with prior exposure to an anthracycline by increasing afterload. Reporting rate of cumulative Cardiac dysfunction post-marketing cases, as of 18-Oct-2018: 3.8 / 1000 PTY (PSUR 4-Table 16-17). [Excludes subjects in clinical trials and compassionate-use programs.] Reversibility: Interruption of pazopanib and/or dose reduction should be combined with treatment of hypertension, if present, in patients with significant reductions in LVEF, as clinically indicated.
Risk factors and risk groups	History of or preexisting cardiac dysfunction. History of or preexisting hypertension (Table 8-6). Concurrent hypertension may exacerbate cardiac dysfunction in patients at risk for increasing cardiac overload. Prior anthracycline therapy (Pai and Nahata 2000, Smith et al 2010).
Preventability	There were no known factors identified to prevent cardiac dysfunction. It is hypothesized that hypertension with a resultant increase in cardiac afterload will exacerbate cardiac dysfunction in patients with subclinical cardiac dysfunction from prior anthracycline exposure. To the extent that this is true, prompt control of blood pressure would be anticipated to reduce the incidence of cardiac dysfunction to some extent. Blood pressure should be well-controlled prior to pazopanib treatment. Patients should be carefully monitored for clinical signs or symptoms of CHF. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction. Specific targeted follow-up checklist continues to collect additional data from future potential cases (Annex 4).
Impact on the benefit-risk balance of the product	Considering the current benefits (Table 1-1), these data continue to support the favorable benefit-risk balance of pazopanib.
Public health impact	Events are manageable and thus, public health impact considered low.

Important Identified Risk: Posterior reversible encephalopathy syndrome (PRES)

Table 8-11 Clinical trial data of PRES

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG105192)			Comparator-controlled clinical study (VEG108844)		
RCC Safety set	Pazopanib N=1140 n (%) 95% CI	Pazopanib N=290 n (%) 95% CI	PBO N=145 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI	Pazopanib N=554 n (%) 95% CI	SUN N=548 n (%) 95% CI	Pazopanib vs. SUN: RR 95% CI
Number of subjects with at least one event	0	0	0	NA	0	0	NA

	Pooled: all clinical studies	Placebo-controlled clinical study (VEG110727)		
STS Safety set	Pazopanib N=382 n (%) 95% CI	Pazopanib N=240 n (%) 95% CI	PBO N=123 n (%) 95% CI	Pazopanib vs. PBO: RR 95% CI
Number of subjects with at least one event	0	0	0	NA

RCC pooled Safety set includes the following clinical studies: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201). STS pooled Safety set includes the following clinical studies: VEG110727, VEG200002.

Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.

NA = RR is not calculated when at least one of the 2 comparison rates was < 5%.

MedDRA Version 20.1, CTCAE Version 3.0, Case Retrieval Strategy Version 15-Feb-2018.

Source: Attachment to Annex 7 of RMP Version 17.0 Table 8-4a, Table 8-4b

Table 8-12 Important identified risk of PRES: Other details

PRES	Details
Potential mechanisms	A possible mechanism can be the failure of the blood-brain barrier to maintain the compartmentalization of intravascular fluid under the influence of the systemic blood pressure (Tlemsani et al 2011).
Evidence sources and strength of evidence	Evidence sources: pazopanib CDP in both therapeutic settings (Table 8-11); PRES safety analysis reported in the GSK safety assessment interval 19-Apr-2012 to 18-Oct-2012; and Novartis' PSUR 1, PSUR 2, PSUR 3, PSUR 4.
Characterization of the risk:	Frequency and severity: in the pazopanib CDP, there were no SAEs of PRES in RCC or STS subjects (Table 8-11). However, PRES was reported as an MRI finding in a case of grade-4 encephalopathy and grade-3 hypertension (Table 8-6). The SAE presented in an 88-year-old [redacted] subject who had taken pazopanib 800 mg/day for 14 days when the dose was reduced to 600 mg/day due to fatigue and headaches. About 5 days after the pazopanib dose reduction, the subject was hospitalized after [redacted] noted [redacted] speech was garbled and [redacted] responsiveness was "poor". Due to a blood pressure of 220/110 mm Hg, the subject was treated with nicardipine drip. Pazopanib was discontinued and the subject improved (RMP Version 16.1-Table 15).

PRES	Details
	PRES has been reported in association with Votrient and can present with headache, hypertension, seizure, lethargy, confusion, blindness, and other visual and neurological disturbances in the Votrient SmPC. Fatal outcome was reported in 1 ovarian, fallopian tube, or peritoneal cancer subject with PRES (GSK document no. 2012N143703_00-Table 1). Reporting rate of cumulative PRES post-marketing cases, as of 18-Oct-2018: 0.5 / 1000 PTY (PSUR 4-Table 16-20). [Excludes subjects in clinical trials and compassionate-use programs.] Reversibility: discontinuation of pazopanib may not be sufficient enough to improve the neurological status of the patient (Tlemsani et al 2011).
Risk factors and risk groups	Groups considered at risk for PRES include females (particularly pregnant patients as PRES has been reported following preeclampsia or eclampsia), middle-aged or older adults on chemotherapy, children with kidney disease or following organ transplantation, and patients with hypoalbuminemia (Shah et al 2012). In patients treated with anti-VEGF agents, it is considered that the risk of PRES is increased "when blood pressure is poorly controlled and when proteinuria is detectable" (Tlemsani et al 2011).
Preventability	Unknown. Permanent discontinuation if evidence of PRES.
Impact on the benefit-risk balance of the product	Considering the current benefits (Table 1-1), these data continue to support the favorable benefit-risk balance of pazopanib.
Public health impact	Events are few and thus, public health impact considered low.

8.3.1.2 Important potential risks

There is currently no important potential risk.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

There is currently no missing information.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Safety topics	
Important identified risks	Hepatic dysfunction Cardiac arrhythmias Hypertension Hypothyroidism Cardiac dysfunction Posterior reversible encephalopathy syndrome (PRES)
Important potential risks	None
Missing information	None

Source: Section 8.3

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

Novartis' routine pharmacovigilance activities include:

- Established processes for the collection and, as required, notification of any AE occurring anywhere in the world, including the EU;
- Established processes for the regular and systematic review of ongoing safety data relating to this pharmaceutical product;
- Permanently and continuously, at its disposal, the services of a Qualified Person responsible for Novartis' pharmacovigilance; and
- Review of additional safety data from ongoing and planned/proposed studies.

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific AE follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below:

- Cardiac dysfunction (Annex 4)

Other forms of routine pharmacovigilance activities:

Not applicable.

10.2 Part III.2. Additional pharmacovigilance activities

None (all additional pharmacovigilance activities have been completed).

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities, as of 11-Jan-2022

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due date
Category 1: Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2: Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Completed				
Category 3: Required additional pharmacovigilance activities				
Completed				

11 Part IV: Plans for post-authorization efficacy studies

Table 11-1 Planned and ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations, as of 10-Feb-2019

Study Status	Summary of primary objectives	Efficacy uncertainties addressed	Milestone	Due date
Efficacy studies which are conditions of the marketing authorization				
Completed				

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Hepatic dysfunction	**Routine risk communication:** SmPC Section 4.2, Section 4.4, Section 4.8 **Routine risk minimization activities recommending specific clinical measure to address the risk:** Liver function should be monitored in SmPC Section 4.4 Dose modification for elevated liver test values in SmPC Table 1 What you need to know in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** None **Legal status:** By medical prescription only
Cardiac arrhythmias	**Routine risk communication:** SmPC Section 4.4, Section 4.8 **Routine risk minimization activities recommending specific clinical measure to address the risk:** Pazopanib should be used with caution in SmPC Section 4.4. ECG monitoring and electrolytes should be maintained within normal range in SmPC Section 4.4. What you need to know in PL Section 2 and Section 4. **Other routine risk minimization measures beyond the Product Information:** None **Legal status:** By medical prescription only
Hypertension	**Routine risk communication:** SmPC Section 4.4, Section 4.8, Section 4.9 **Routine risk minimization activities recommending specific clinical measure to address the risk:** Blood pressure should be well controlled in SmPC Section 4.4. Hypertension should be monitored early and frequently after starting pazopanib in SmPC Section 4.4. Dose interruption/reduction combined with antihypertensives in SmPC Section 4.4. Dose discontinuation if hypertensive crisis in SmPC Section 4.4. What you need to know in PL Section 2 and Section 4.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information:
	None
	Legal status:
	By medical prescription only
Hypothyroidism	**Routine risk communication:**
	SmPC Section 4.4, Section 4.8
	Routine risk minimization activities recommending specific clinical measure to address the risk:
	Thyroid function test should be performed at baseline and periodically after starting pazopanib in SmPC Section 4.4.
	What you need to know in PL Section 4.
	Other routine risk minimization measures beyond the Product Information:
	None
	Legal status:
	By medical prescription only
Cardiac dysfunction	**Routine risk communication:**
	SmPC Section 4.4 and Section 4.8
	Routine risk minimization activities recommending specific clinical measure to address the risk:
	Concurrent hypertension may exacerbate cardiac dysfunction, increasing cardiac afterload; prior anthracycline therapy in Section 4.4.
	Carefully monitor for signs and symptoms of CHF; baseline and periodic LVEF evaluations are recommended in Section 4.4.
	What you need to know in PL Section 4.
	Other routine risk minimization measures beyond the Product Information:
	None
	Legal status:
	By medical prescription only
Posterior reversible encephalopathy syndrome (PRES)	**Routine risk communication:**
	SmPC Section 4.4 and Section 4.8
	Routine risk minimization activities recommending specific clinical measure to address the risk:
	PRES can present with headache, hypertension, seizure, lethargy, confusion, blindness, and other visual and neurological disturbances in Section 4.4
	What you need to know in PL Section 4.
	Other routine risk minimization measures beyond the Product Information:
	None
	Legal status:
	By medical prescription only

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Hepatic dysfunction	**Routine risk minimization measures:** SmPC Section 4.2, Section 4.4, Section 4.8 SmPC Section 4.4 where advice is given on monitoring of liver function SmPC Table 1 where advice is given on dose modification for elevated liver test values PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Cardiac arrhythmias	**Routine risk minimization measures:** SmPC Section 4.4, Section 4.8 SmPC Section 4.4 where advice is given on caution with pazopanib SmPC Section 4.4 where advice is given on monitoring of ECG and maintenance of electrolytes within normal range PL Section 2 and Section 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Hypertension	**Routine risk minimization measures:** SmPC Section 4.4, Section 4.8, Section 4.9 SmPC Section 4.4 where advice is given on controlling blood pressure SmPC Section 4.4 where advice is given on monitoring early and frequently hypertension after starting pazopanib SmPC Section 4.4 where advice is given on dose interruption/reduction combined with antihypertensives SmPC Section 4.4 where advice is given on dose discontinuation if hypertensive crisis PL Section 2 and Section 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Hypothyroidism	**Routine risk minimization measures:** SmPC Section 4.4, Section 4.8 SmPC Section 4.4 where advice is given on thyroid function test being performed at baseline and periodically after starting pazopanib PL Section 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Cardiac dysfunction	**Routine risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	SmPC Section 4.4, Section 4.8 SmPC Section 4.4 where advice is given on concurrent hypertension that may exacerbate cardiac dysfunction, increasing cardiac afterload; and further, advice on prior anthracycline therapy SmPC Section 4.4 where advice is given on monitoring carefully for signs and symptoms of CHF; and further, advice on baseline and periodic LVEF evaluations PL Section 4	**reactions reporting and signal detection:** AE follow-up form for adverse reaction **Additional pharmacovigilance activities:** None
Posterior reversible encephalopathy syndrome (PRES)	**Routine risk minimization measures:** SmPC Section 4.4 and Section 4.8 SmPC Section 4.4 where advice is given on the presentation of PRES as headache, hypertension, seizure, lethargy, confusion, blindness, and other visual and neurological disturbances PL Section 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

13 Part VI: Summary of the risk management plan for Votrient (pazopanib)

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

Votrient's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Votrient should be used.

This summary of the RMP for Votrient 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 Votrient's RMP.

13.1 Part VI: I. The medicine and what it is used for

Votrient is authorized for both:

1. Advanced renal cell carcinoma and for patients who have received prior cytokine therapy for advanced disease, as first-line
2. Selective subtypes of advanced soft tissue sarcoma who have received prior chemotherapy for metastatic disease or who have progressed within 12 mo after (neo) adjuvant therapy. Efficacy and safety have only been established in certain STS histological tumor subtypes

It contains pazopanib as the active substance and it is given by oral route of administration, also known as by mouth.

Further information about the evaluation of Votrient's benefits can be found in Votrient's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to Votrient's EPAR summary landing page on the EMA webpage: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/001141/WC500094273.pdf (Accessed 02-Oct-2018).

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized 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 minimize its risks.

Together, these measures constitute **routine risk minimization** measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, 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 Votrient is not yet available, it is listed under **missing information** below.

13.2.1 Part VI: II.A: List of important risks and missing information

Important risks of Votrient are risks that need special risk management activities to further investigate or minimize 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 Votrient. 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 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Hepatic dysfunction Cardiac arrhythmias Hypertension Hypothyroidism Cardiac dysfunction Posterior reversible encephalopathy syndrome (PRES)
Important potential risks	None
Missing information	None

13.2.2 Part VI: II.B: Summary of important risks

Table 13-2 Important identified risk: Hepatic dysfunction

Evidence for linking the risk to the medicine	Supporting data are referenced in the CSRs for the following clinical studies: RCC: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201) STS: VEG110727, VEG200002
Risk factors and risk groups	History of alcoholism, nonalcoholic fatty liver disease, viral hepatitis, or hepatic metastases. However, RCC in the absence of hepatic metastases: paraneoplastic syndromes with hepatic-related manifestations, e.g. Stauffer syndrome. Ages approaching elderly age group: ≥ 60-year-olds.

	Known genetic polymorphisms: HLA-B*57:01 allele carrier. Concomitant use with hepatotoxic drug; concomitant use with simvastatin.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2, Section 4.4, Section 4.8 **Additional risk minimization measures** No risk minimization measures

Table 13-3 Important identified risk: Cardiac arrhythmias

Evidence for linking the risk to the medicine	Supporting data are referenced in the CSRs for the following clinical studies: RCC: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201) STS: VEG110727, VEG200002
Risk factors and risk groups	Long QT syndrome (LQTS) or relevant pre-existing cardiac disease. History of QT prolongation. Obesity, hypertension, smoking, dyslipidemia, or in elderly (> 65-year-olds) patients; any other factors/groups associated with ischemic cardiac disease. Electrolyte disturbances of magnesium, potassium, or calcium. Drug or agent known to increase risk of cardiac arrhythmia, e.g. anthracyclines, thoracic radiation therapy. Drug known to prolong the QT interval, e.g. antiarrhythmics.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4, Section 4.8 **Additional risk minimization measures** No risk minimization measures

Table 13-4 Important identified risk: Hypertension

Evidence for linking the risk to the medicine	Supporting data are referenced in the CSRs for the following clinical studies: RCC: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201) STS: VEG110727, VEG200002 Evidence: pooled meta-analysis on pazopanib 800 mg/day of 13 clinical studies in cancer patients (N=1651): overall incidence of hypertension, all grades, 35.9% (95% CI: 31.5, 40.6), grade 3/4, 6.5% (5.2, 8.0); overall risk of hypertension, all grades, RR=4.97 (3.38, 7.30; $p < 0.001$), grade 3/4, RR=2.87 (1.16, 7.12; p=0.023). No statistical difference between RCC vs. non-RCC (all grades, RR=1.21; 95% CI: 0.96,

	1.53; p=0.11 // grade 3/4, 1.29; 0.80, 2.07; p=0.30).
Risk factors and risk groups	Hyperlipidemia, obesity and/or DM, smoking, and alcoholism. Patients with significant reductions in LVEF or at risk of cardiac dysfunction. History of or preexisting hypertension.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4, Section 4.8, Section 4.9 **Additional risk minimization measures** No risk minimization measures

Table 13-5 Important identified risk: Hypothyroidism

Evidence for linking the risk to the medicine	Supporting data are referenced in the CSRs for the following clinical studies: RCC: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201) STS: VEG110727, VEG200002
Risk factors and risk groups	Prior history of thyroid dysfunction.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4, Section 4.8 **Additional risk minimization measures** No risk minimization measures

Table 13-6 Important identified risk: Cardiac dysfunction

Evidence for linking the risk to the medicine	Supporting data are referenced in the CSRs for the following clinical studies: RCC: VEG105192 (Study A2303), VEG102616, VEG107769, VEG108844 (Study A2301), VEG113078 (Study A2201) STS: VEG110727, VEG200002
Risk factors and risk groups	History of or preexisting cardiac dysfunction. History of or preexisting hypertension. Concurrent hypertension may exacerbate cardiac dysfunction in patients at risk for increasing cardiac overload. Prior anthracycline therapy.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4, Section 4.8 **Additional risk minimization measures** No risk minimization measures

Table 13-7 Important identified risk: Posterior reversible encephalopathy syndrome (PRES)

Evidence for linking the risk to the medicine	Evidence sources: pazopanib CDP in both therapeutic settings; PRES safety analysis reported in the GSK safety assessment interval

	19-Apr-2012 to 18-Oct-2012; and Novartis' PSUR 1, PSUR 2, PSUR 3, PSUR 4.
Risk factors and risk groups	Groups considered at risk for PRES include females (particularly pregnant patients as PRES has been reported following preeclampsia or eclampsia), middle-aged or older adults on chemotherapy, children with kidney disease or following organ transplantation, and patients with hypoalbuminemia. In patients treated with anti-VEGF agents, it is considered that the risk of PRES is increased "when blood pressure is poorly controlled and when proteinuria is detectable".
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4, Section 4.8 **Additional risk minimization measures** No risk minimization measures

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Votrient.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

None are currently proposed.

14 Part VII: Annexes

Annex 4 – Specific adverse drug reaction follow-up forms

Cardiac dysfunction

Cardiac dysfunction / LVEF decrease (Version 1.0 / Sep-2015)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:

Was the cardiac dysfunction/ejection fraction decrease: ☐ symptomatic ☐ asymptomatic

If symptomatic, please **check all that apply:**

☐ Shortness of breath (dyspnea) ☐ Ascites

☐ Orthopnea ☐ Spontaneous weight gain

☐ Chest discomfort (pain, pressure, heaviness, tightness) ☐ Fatigue

☐ Peripheral edema ☐ Cough

☐ Jugular venous distension or S3 gallop rhythm ☐ Palpitations

☐ Hypertension ☐ Nausea

☐ Pulmonary edema ☐ Lack of appetite

☐ None of the above

Yes **No**

Did the patient have hypertension (BP > 140/90 mmHg) within 1 month of/in relation of the event? ☐☐

Was pazopanib therapy interrupted?☐☐

Was the dose of pazopanib reduced?☐☐

Did the patient receive treatment for heart failure?☐☐

If yes, please provide details of therapy: _____

Did the patient recover?☐☐

Was pazopanib resumed at recovery?☐☐

If yes, please provide details of therapy: _____

Diagnostic Tests (please attach all applicable):

What were LVEF results:Attached ☐

Please attach the reports if available:ECHOMUGAOther-Specify Date

LVEF before the event: ____% ____ LLN* % ☐☐☐ _____

LVEF at the time of the event: ____% ____ LLN* % ☐☐☐ _____

LVEF at resolution or last FU: ____% ____ LLN* % ☐☐☐ _____

*LLN: Institutional lower limit of normal

Were any of the following diagnostic tests performed? **Check all that apply and specify including dates and results**

☐ ECG ☐ Stress/Exercise test

☐ Cardiac catheterization (i.e. pressure, visualization, ☐ Blood tests (e.g. electrolytes, cardiac angiography, coronarography)enzymes, BNP, etc.)

☐ Chest x-ray/CT ☐ None of the above

Patient History:

Did the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply**

☐ Heart failure ☐ Arrhythmias (atrial or ventricular) ☐ Heart tumor

☐ Coronary artery disease ☐ Diabetes☐ Thrombotic disease

☐ Congenital heart disease ☐ Valvular heart disease (regurgitation or ☐ Heavy alcohol use

☐ Carditis (any type)stenosis) ☐ Heavy caffeine

☐ Anemia (Grade 3 or 4) ☐ Hypertrophic Obstructiveconsumption

☐ Left ventricular hypertrophyCardiomyopathy (HOCM) ☐ Hyperthyroidism

☐ Hypertension ☐ Malnutrition ☐ Hypothyroidism

☐ Sleep apnea ☐ Aorta aneurysm ☐ Smoking

☐ Other relevant history *(please specify)* ☐ Tumour lesions in the heart or lesions compressing the heart?

☐ None of the above

Was the patient taking any of the following drugs? **Check all that apply**

☐ Radiation therapy (if yes, provide total dose: _____) ☐ Cocaine or other drugs of abuse

☐ Chemotherapy/Cardiotoxic medication (e.g. anthracycline) ☐ Other Cardiovascular therapy *(please specify)*

☐ Vitamin E overuse ☐ None of the above

Annex 6 – Details of proposed additional risk minimization activities

Not applicable.