Votrient

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
N/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/04/2023		PL	
II/0071/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch	01/09/2022	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change				

	in the manufacturing process B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.a.1.z - Change in the manufacturer of AS or of a				

	starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IAIN/0074	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	13/06/2022	n/a		
PSUSA/2321/202110	Periodic Safety Update EU Single assessment - pazopanib	10/06/2022	n/a		PRAC Recommendation - maintenance
IB/0073	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/03/2022	n/a		
II/0068	C.I.4 - Change(s) in the SPC, Labelling or PL due to	07/10/2021	08/07/2022	SmPC and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0070	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	30/09/2021	08/07/2022	Annex II and PL	
IA/0069	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	06/09/2021	n/a		
II/0067/G	This was an application for a group of variations. C.I.4 Update of section 4.8 of the SmPC in order to add hepatic failure to the list of adverse reactions reported in patients with soft tissue sarcoma (STS)with the frequency not known. The Package Leaflet is updated accordingly. C.I.4 Update of section 4.4 of the SmPC in order to update the information on studies with pazopanib in combination with other systemic anti-cancer therapies which were terminated early due to concerns over increased toxicity and/or mortality. Type IA A.6 Update of section 5.1 of the SmPC with the updated ATC code L01EX03 released by WHO.	10/06/2021	08/07/2022	SmPC and PL	Cases of hepatic failure have been reported in patients with STS during use of pazopanib. Clinical studies of pazopanib in combination with a number of other anti-cancer therapies (including for example pemetrexed, lapatinib or pembrolizumab) were terminated early due to concerns over increased toxicity and/or mortality, and a safe and effective combination dose has not been established with these regimens. For more information, please refer to the Summary of Product Characteristics.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/2321/ 202010	Periodic Safety Update EU Single assessment - pazopanib	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0066	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/05/2021	n/a		
IB/0064/G	This was an application for a group of variations. B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished	27/01/2021	n/a		

	product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient				

	- Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products				
II/0063/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name	21/01/2021	n/a		

	and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for				

	the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a				

	re-test period/storage period supported by real time data				
II/0059	To update sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on results from studies 2012-001306-20 (ADVL0815 / PZP114411) and study 2013-003595-12 (ADVL1322 / VEG116731 / PZP034X2203) listed in the agreed PIP; these are a phase 1 clinical trial of single-agent pazopanib in children with a relapsed or refractory solid (including CNS) tumour, and a therapeutic-exploratory (phase 2) clinical trials of single-agent pazopanib in children (including adolescents) and young adults with a refractory tumour. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/11/2020	17/12/2020	SmPC	SmPC new text Paediatric population Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made. A Phase I study (ADVL0815) of pazopanib was conducted in 44 paediatric patients with various recurrent or refractory solid tumours. The primary objective was to investigate the maximum tolerated dose (MTD), the safety profile and the pharmacokinetic properties of pazopanib in children. A Phase II study (PZP034X2203) of pazopanib was conducted in 57 paediatric patients with refractory solid tumours including rhabdomyosarcoma (N=12), non-rhabdomyosarcoma soft tissue sarcoma (N=11), Ewing sarcoma/pPNET (N=10), osteosarcoma (N=10), neuroblastoma (N=8) and hepatoblastoma (N=6). Results of this study did not show any meaningful anti-tumour activity in the respective paediatric population. Pazopanib is therefore not recommended for treatment of these tumours in the paediatric population. The safety profile in paediatric patients was similar to that reported with pazopanib in adults in the approved indications based on data from 44 paediatric patients from Phase I study ADVL0815 and 57 paediatric patients from Phase II study PZP034X2203. For more information, please refer to the Summary of Product Characteristics.

IAIN/0062/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	16/10/2020	17/12/2020	Annex II and PL	
IB/0061	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/10/2020	17/12/2020	SmPC and PL	
PSUSA/2321/201910	Periodic Safety Update EU Single assessment - pazopanib	28/05/2020	27/07/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2321/201910.
IB/0060	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	17/07/2020	17/12/2020	SmPC	
IAIN/0058/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	07/02/2020	27/07/2020	Annex II and PL	

	finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				

	A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IA/0056	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/11/2019	27/07/2020	SmPC and PL	
II/0054	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	05/09/2019	n/a		
PSUSA/2321/ 201810	Periodic Safety Update EU Single assessment - pazopanib	16/05/2019	n/a		PRAC Recommendation - maintenance
IAIN/0052/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	04/01/2019	n/a		

	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms				
IB/0051	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	16/11/2018	n/a		
II/0050	Submission of the final report from the observational study PZP034A2401 'A prospective observational study of real world treatment patterns and treatment outcomes in patients with advanced or metastatic renal cell carcinoma receiving pazopanib'. This study is listed as a category 3 study in the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	04/10/2018	n/a		
II/0049	Submission of the final report from the non-interventional post-authorisation safety study PZP034AKR02 to monitor the safety and effectiveness of Votrient in Korea. This study is listed as a category 3 study in the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	04/10/2018	n/a		
IG/0950	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	18/06/2018	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release)				
IA/0047	B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	06/06/2018	n/a		
PSUSA/2321/ 201710	Periodic Safety Update EU Single assessment - pazopanib	17/05/2018	n/a		PRAC Recommendation - maintenance
T/0046	Transfer of Marketing Authorisation	26/03/2018	08/05/2018	SmPC, Labelling and PL	
IB/0044/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	26/02/2018	n/a		

	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0043	Update of section 4.8 of the SmPC in order to update the frequency of the adverse drug reaction 'infection' from uncommon to common. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct some discrepancies in sections 4.4, 4.5 and 4.8 of the SmPC. The PL is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/01/2018	08/05/2018	SmPC and PL	
R/0042	Renewal of the marketing authorisation.	09/11/2017	08/01/2018	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Votrient in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/2321/ 201610	Periodic Safety Update EU Single assessment - pazopanib	05/05/2017	n/a		PRAC Recommendation - maintenance

IB/0041	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/01/2017	n/a		
II/0039	Update of section 4.8 to add the adverse reaction Polycythaemia with the frequency uncommon. This variation, based on cumulative review of all cases, is provided following the PRAC request on the signal assessment report EPITT no 18660. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	11/09/2017	SmPC and PL	
II/0038	Update of SmPC section 4.6 to add male contraception wording following a review of pazopanib according to the MAH's guideline on prevention of pregnancies. The Package Leaflet is proposed to be updated accordingly. An updated RMP version 16 is agreed. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template version 10 and combine the SmPC of the 2 tablets strengths. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/10/2016	11/09/2017	SmPC, Annex II, Labelling and PL	In line with the MAH guideline on prevention of pregnancies, considering that pazopanib is teratogenic and exposure to a foetus via a male partner during intercourse could pose a risk to the foetus, it has been agreed to add wording regarding the use of condoms in male patients in section 4.6 of the SmPC. The PL was updated accordingly.
IA/0037/G	This was an application for a group of variations.	21/07/2016	n/a		

	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites				
PSUSA/2321/ 201510	Periodic Safety Update EU Single assessment - pazopanib	13/05/2016	n/a		PRAC Recommendation - maintenance
IAIN/0036/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	12/05/2016	n/a		

	site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a				

	manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IB/0035/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	06/04/2016	n/a		
II/0033	Update of section 4.4 and 5.1 of the SmPC in order to update pharmacogenomics information following meta-data analysis (study number 201761) of additional clinical trials. In addition, the MAH took the opportunity to add footnote in Table 3 in section 4.8 of the SmPC to align with Table 2 of the same section. Moreover, the revised RMP version 15.1 has been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	14/07/2016	SmPC	Based on the data from the study "PGx7610: Genetic Evaluation of Hepatotoxicity in Pazopanib Studies" which show an increased risk of ALT elevations in pazopanib-treated patients, sections 4.4 and 5.1 of the SmPC are updated to provide more detailed information regarding patients with the HLA-B*57:01 genotype.
II/0032/G	This was an application for a group of variations. Update of section 5.3 of the SmPC in order to update	17/12/2015	14/07/2016	SmPC	

	safety information following completion of two carcinogenicity studies in mice and rats. In addition, the MAH submitted a study on the induction of cytochrome P450 (CYP) mRNA expression in mice. Moreover, the revised RMP version 15 has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/2321/ 201410	Periodic Safety Update EU Single assessment - pazopanib	21/05/2015	17/07/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2321/201410.
IAIN/0031/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	13/07/2015	14/07/2016	Annex II and PL	

T/0030	Marketing Authorisation Transfer from Glaxo Group Ltd. to Novartis Europharm Limited. Transfer of Marketing Authorisation	30/03/2015	05/05/2015	SmPC, Labelling and PL	
II/0029/G	This was an application for a group of variations. Based on clinical trials and the MAH's safety review, update of wording of sections 4.4 and 4.8 of SmPC to add Interstitial Lung Disease(ILD)/Pneumonitis. The PL has been updated accordingly. Following the study VEG 108844 results, update of section 4.4 of SmPC to add more information on myocardial dysfunction. Following the review of safety data from the sarcoma studies, update of section 4.4 of SmPC to correct the number of reported cases of Congestive Heart Failure. The RMP has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	23/04/2015	17/07/2015	SmPC and PL	

	data				
II/0027/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information with regards to hepatic function, adverse events in the Asian population and the risk of retinal tears and retinal detachment. In addition, the MAH took the opportunity to update the allocated frequency categories for existing ADRs in section 4.8 of the SmPC. The Package Leaflet is updated accordingly. A revised RMP version 12 was provided as part of the application. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	15/01/2015	SmPC and PL	All proposed changes to the Votrient product information included in this variation are supported by ongoing Pharmacovigilance monitoring by the MAH as well as results and conclusions drawn from clinical studies previously submitted. In addition to these safety evaluations, a routine review of the Votrient product information and the Risk Management Plan was performed.
II/0026	Update of section 4.2 of the SmPC further to submission of the results of Study ADVL0815 (PZP114411), a Phase I Study of Pazopanib as a Single Agent for Children with Relapsed or Refractory Solid Tumours, including central nervous system (CNS) tumours.	20/11/2014	15/01/2015	SmPC	Please refer to the Scientific Discussion H-1141-VAR-II-26 for Votrient.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0025	Update of section 5.1 of the SmPC in order to update the efficacy information based on the final study report for study VEG108844. In addition PAM-ANX-012 and PAM-REC-011 have been fulfilled and Annex II has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	15/01/2015	SmPC and Annex II	In this variation section 5.1 of the SmPC has been updated with efficacy results based on the final study report for VEG108844. The final overall survival (OS) analysis confirms the primary analysis. The HR is 0.915 and the final median OS is 28.3 months in the pazopanib arm and 29.1 months in the sunitinib arm. At the time of the final analysis a majority of subjects (60%) had died, compared to 46% at time of the primary analysis. Non-inferiority of pazopanib to sunitinib has been comfirmed. With regard to safety, no new safety signals for pazopanib were observed, and the safety profile of pazopanib is consistent previous findings. In addition, the MAH has submitted an additional clinical study report on biomarkers from study VEG108844 in order to provide detailed analysis on biomarkers and genetic aberrations with correlations to clinical response to pazopanib or sunitinib. Due to a very limited number of patients in each subgroup, any interpretation of data is impossible.
PSUV/0024	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
II/0023	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2013	15/01/2015	SmPC and PL	

II/0018	Update of section 4.4 of the SmPC in order update the safety information to include the need for earlier and more frequent liver toxicity monitoring based on new safety data from study VEG108844. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI has been updated according to the latest QRD template version 9. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	01/07/2013	SmPC and PL	In this variation the MAH has updated section 4.4 of the SmPC in order to include the need for earlier and more frequent liver toxicity monitoring based on new safety data from study VEG108844. Serum liver tests should be monitored before initiation of treatment with pazopanib and now at weeks 3, 5, 7 and 9. Thereafter, monitored at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring should then continue after Month 4.
R/0017	Renewal of the marketing authorisation.	21/03/2013	14/06/2013	SmPC, Annex II and PL	The CHMP considered that, as all Specific Obligations have been fulfilled, there are no remaining grounds for the Marketing Authorisations to remain conditional.
IAIN/0021	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	19/04/2013	n/a		
IG/0279	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2013	01/07/2013	SmPC, Labelling and PL	
II/0016/G	This was an application for a group of variations. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	13/12/2012	03/05/2013	SmPC and PL	

	clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
II/0015	Update of sections 4.4 and 4.5 of the SmPC in order to add information on the interaction of pazopanib with irinotecan when administered in combination with cetuximab based on results from study VEG108925. These changes were requested further to the assessment of follow up measure FU2 008.1. C.I.3.z - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation	20/09/2012	24/10/2012	SmPC	Results from study VEG108925, a Phase I, open-label, study of the safety, tolerability, and pharmacokinetics of pazopanib in combination with irinotecan and cetuximab, indicated that co-administration of pazopanib and irinotecan increased systemic exposure to both the parent drug and the active metabolite, SN-38. Section 4.4 of the currently approved SmPC already includes a warning based on in vitro data. This existing warning is being further substantiated with pharmacokinetic data and observed interactions from study VEG108925 under section 4.5.
II/0014	Update of section 4.5 of the SmPC in order to add information on interaction with esomeprazole further to the results of a study conducted to fulfil FUM 007. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial change to section 4.2 of the SmPC. C.I.4 - Variations related to significant modifications	19/07/2012	30/08/2012	SmPC and PL	Results from pharmacokinetic study VEG113971 suggested that the co-administration of esomeprazole 40 mg and pazopanib 800 mg daily resulted in a decrease in AUC(0-24) and Cmax of about 40% and 42% respectively, relative to the administration of pazopanib alone 800 mg. No new or unexpected AEs were reported. In view of these results, section 4.5 of the SmPC has been updated to avoid the co-adminiostration of pazopanib with medicines that raise

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				gastric pH. If the concomitant use of a proton-pump inhibitor (PPI) is medically necessary, it is recommended that the dose of pazopanib be taken without food once daily in the evening concomitantly with the PPI. If the concomitant administration of an H2-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H2-receptor antagonist. Pazopanib should be administered at least 1 hour before or 2 hours after administration of short-acting antacids. The recommendations for how PPIs and H2-receptor antagonists are co-administered are based on physiological considerations.
II/0007	Update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC in order to extend the indication of Votrient for the treatment of patients with advanced Soft Tissue Sarcoma (STS). The Package Leaflet is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/05/2012	03/08/2012	SmPC, Annex II and PL	Please refer to Assessment Report H-1141-AR-II-07-en.
II/0011	Update of sections 4.4 and 4.5 of the Summary of the Product characteristic (SmPC) to include information on interaction with ketoconazole, following the assessment of final study report for study VEG113971 (an open-label study in cancer patients to evaluate the effects of ketoconazole and the effects of increased gastric pH on the pharmacokinetics of orally administered pazopanib).	19/04/2012	25/05/2012	SmPC, Labelling and PL	Results from pharmacokinetic study VEG113971 suggest that the co-administration of ketoconazole 400 mg and pazopanib 400 mg daily resulted in an increase in AUC(0-24) and Cmax of about 66% and 45% respectively, relative to the administration of pazopanib alone 400 mg. There were a relative higher proportion of patients reporting drug-related adverse events during concomitant treatment with ketoconazole (13/21) more than during treatment with

	This variation application addresses partly Follow Up Measure (FUM) 007. Furthermore, the Marketing Authorisation Holder (MAH) took this opportunity to update the list of local representatives in the Patient Leaflet (PL) and to bring the Product Information (PI) in line with the latest Quality Review of Documents (QRD) template (version 8.1, October 2011). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				pazopanib alone (8/21). No patient (0/21) experienced any hyperglycaemia when receiving pazopanib only, while the incidence was 8/21 when concomitantly receiving ketoconazole. These observations are plausibly related to the increased exposure during concomitant with treatment with ketoconazole. Therefore, section 4.5 of the SmPC has been updated to avoid the concomitant use of pazopanib with a strong Cytochrome P-450 (CYP) 3A4 inhibitor such as ketoconazole. If no medically acceptable alternative is available, the dose of pazopanib should be reduced to 400 mg daily during concomitant administration and attention to adverse drug reaction should be intensified. Furthermore a caution was implemented in section 4.4 of the SmPC to reflect the risk of hyperglycaemia during concomitant treatment with ketoconazole.
R/0012	Renewal of the marketing authorisation.	15/03/2012	22/05/2012	Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Votrient, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion. The CHMP requested the PSUR to be submitted on half-yearly cycle.
IG/0150/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	05/04/2012	n/a		

	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0009	Update of sections 4.2, 4.3, 4.4 and 5.2 of the SmPC in order to include updated recommendations and pharmacokinetic data in hepatic impaired patients based on the results from the final report of study NCI 8063 (VEG110827). This variation application addresses Follow Up Measure (FUM) 006. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/02/2012	19/03/2012	SmPC	Based on the final results from pharmacokinetic study NCI 8063 (VEG110827) the Maximum tolerated Dose (MTD) of pazopanib was determined to be 800 mg once daily for patients with mild liver dysfunction and 200 mg once daily in patients with moderate or severe liver dysfunction. Moreover, the median steady-state Cmax and AUC(0-24) values after administration of 200 mg pazopanib once daily in patients with moderate hepatic impairment were approximately 44 % and 39 %, of the corresponding median values after administration of 800 mg once daily in patients with normal hepatic function, respectively. In patients with severe hepatic impairment the median steady-state Cmax and AUC(0-24) values after administration of 200 mg pazopanib once daily were approximately 18 % and 15 %, of the corresponding median values after administration of 800 mg once daily in patients with normal hepatic function. Results from the study indicated that pazopanib 200 mg once daily will not achieve therapeutic plasma pazopanib concentrations in patients with severe hepatic impairment, therefore pazopanib in patients with severe hepatic impairment is not recommended. Based on the above, the SmPC has been revised to include recommendations and pharmacokinetic data in hepatic impaired patients.

II/0008	Update of Section 5.1 of the SmPC to include results from the final overall survival analysis from study VEG105192, proposed by the MAH further to the assessment of FUM 009. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	24/10/2011	SmPC	In this variation the MAH has updated section 5.1 of the SmPC to include results from the final overall survival analysis from study VEG105192. The SmPC is being amended to include data that were not previously available from the pivotal trial in patients with RCC. The main changes include updates of the overall survival, the percent of patients in the placebo arm who crossed over and were treated with pazopanib after progression and the percent of patients in the placebo and pazopanib arms who received post-study therapy.
II/0006	Update of section 4.4 of the SmPC on the increased toxicity and mortality observed when used in combination with the anti-cancer medicinal products premetrexed and lapatinib based on the findings from studies VEG111128 and VEG105281, respectively, and update of sections 4.4 and 4.8 of the SmPC to include information on the risk of serious infections. These changes were requested further to the assessment of PSUR 1. The PL has been updated accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	22/09/2011	24/10/2011	SmPC and PL	In this variation the MAH has revised section 4.4 of the SmPC to include a warning on the increased toxicity and mortality observed when used in combination with the anti-cancer medicinal products premetrexed and lapatinib based on the findings from clinical studies that were terminated early due to this reason. A safe and effective combination dose has not been established with these regimens. In addition, sections 4.4 and 4.8 have also been updated to include informationon the risk of serious infections (with or without neutropenia) and in some cases with fatal outcome, seen in patients receiving pazopanib. These changes were requested by CHMP further to the assessment of PSUR 1. The PL has been updated accordingly.
II/0005	Update of sections 4.4 and 4.5 of the SmPC on the increased risk of alanine aminotransferase (ALT) elevations in the case of concomitant use with	22/09/2011	24/10/2011	SmPC and PL	In this variation the MAH has revised sections 4.4 and 4.5 of the SmPC to include updated safety information on the concomitant use of pazopanib and simvastatin. Results

	simvastatin and other statins based on the results of a meta-analysis in eleven clinical studies (VEG115003). The PL has been updated accordingly. In addition the MAH took the opportunity to update the date of the latest renewal in section 9 of the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				from a meta-analysis in eleven clinical studies (VEG115003) have shown that concomitant use of pazopanib and simvastatin increased the risk of ALT elevations (14 % of patients who did not use statins, compared with 27 % patients who had concomitant use of simvastatin). In addition, concomitant use of pazopanib and other statins should be also undertaken with caution as there are insufficient data are available to assess their impact on ALT levels. It can not be excluded that pazopanib will affect the pharmacokinetics of other statins (e.g. atorvastatin, fluvastatin, pravastatin, rosuvastatin).
IA/0004	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	06/06/2011	n/a		
R/0003	Renewal of the marketing authorisation.	17/02/2011	06/05/2011	Annex II	Renewal of the marketing authorisation
II/0001	Update of sections 4.2, 4.4 and 5.2 of the SmPC to provide updated recommendation for patients with mild hepatic impairment further to new pharmacokinetic data available in this patient population. In addition minor editorial amendments have been implemented in the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/03/2011	02/05/2011	SmPC	In this variation the MAH has updated the recommendations for the use of pazopanib in patients with mild hepatic impairment in sections 4.2 and 4.4 of the SmPC further to the assessment of the interim results of the Phase I pharmacokinetic study PhI-60 (NCI Protocol 8063). It is recommended that patients with mild abnormalities in liver parameters (defined as either normal bilirubin and any degree of alanine aminotransferase (ALT) elevation or as an elevation of bilirubin (> 35 % direct) up to 1.5 x upper limited of normal (ULN) regardless of the ALT value) are treated initially with 800 mg pazopanib once

					daily. In addition, PK information in section 5.2 of the SmPC has been updated to reflect the new results.
II/0002	Changes in section 4.4 of the SmPC to reflect updated recommendations on the risk of hypertension following the evaluation of reports of hypertension from the MAH safety database and the renal cell carcinoma (RCC) clinical trial population. In addition, the date of first authorization has been included in the SmPC and marketing authorisation numbers have been included in the SmPC and Labelling. Finally, minor editorial changes have been implemented in the SmPC and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	01/02/2011	SmPC, Labelling and PL	In this type II variation the MAH updated section 4.4 of the SmPC following the evaluation of updated information on reports of hypertensive crisis from the MAH clinical safety database and analysis of the cumulative incidence of hypertension by day 9 in the renal cell carcinoma (RCC) clinical trials population. The existing warning regarding hypertension was amended to indicate that events of hypertension including newly diagnosed symptomatic episodes of elevated blood pressure (hypertensive crisis) have occurred on treatment with pazopanib. The warning includes that elevated blood pressure may occur early (39% of patients who experienced it did so by day 9 of treatment). Finally recommendations on the need to discontinue pazopanib treatment if there is evidence of persistently elevated values of blood pressure (140/90 mmHg) or if arterial hypertension is severe and persists despite anti-hypertensive therapy and pazopanib dose reduction have been included.
IG/0034/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the	06/01/2011	n/a	Annex II	

	major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				