Vargatef

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
WS/2701	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to add 'posterior reversible encephalopathy	04/07/2024		SmPC and PL	SmPC new text With this variation the MAH submitted an update of the Summary of Product Characteristics (SmPC) based on an identified signal of Posterior reversible encephalopathy syndrome (PRES) during the continues safety screen of Ofev®. Based on this, literature and the labels of other

[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).

	syndrome (PRES)' to the list of adverse drug reactions (ADRs) with frequency 'Not known' based on postmarketing data and literature. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and update the list of representatives. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				drugs that have an inhibitory activity on the VEGF pathway were reviewed. Considering the available evidence and that PRES is a recognised known side effect of VEGF inhibitors, sections 4.4 and 4.8 of the SmPC are updated. The Package Leaflet is updated accordingly. Section 4.4 includes a warning regarding PRES to indicate that some cases of PRES have been reported in post-marketing, have been reported with other VEGF inhibitors, and that if PRES is suspected, nintedanib treatment must be discontinued. Reinitiating nintedanib therapy in patients previously experiencing PRES is not known and should be left to the physician's recommendation. Section 4.8 was updated in order to add 'Posterior reversible encephalopathy syndrome (PRES)' to the list of adverse drug reactions (ADRs) with frequency 'Not known'. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and updated the list of representatives. For more information, please refer to the Summary of Product Characteristics.
IB/0052/G	This was an application for a group of variations. 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.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	11/04/2024		SmPC and PL	

	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.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings				
IB/0051	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	26/03/2024	n/a		

IB/0050/G	This was an application for a group of variations. 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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	03/11/2023	n/a		
PSUSA/10318 /202210	Periodic Safety Update EU Single assessment - nintedanib (oncology indications)	22/06/2023	23/08/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10318/202210.
IG/1639/G	This was an application for a group of variations. B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-	25/07/2023	n/a		

	significant specification parameter (e.g. deletion of an obsolete parameter) 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)				
II/0047/G	This was an application for a group of variations. 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	22/06/2023	23/08/2023	SmPC and PL	
II/0044	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	07/07/2022	n/a		
IG/1505/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.c.2.a - Change in test procedure for an excipient - 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	03/06/2022	n/a		

	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 A.7 - Administrative change - Deletion of manufacturing sites B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites				
IB/0045/G	This was an application for a group of variations. B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation B.II.c.z - Change in control of excipients in the Finished Product - Other variation 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	28/02/2022	n/a		
IG/1463	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	18/11/2021	09/11/2022	SmPC, Labelling and PL	
N/0042	Minor change in labelling or package leaflet not	04/10/2021	09/11/2022	PL	

	connected with the SPC (Art. 61.3 Notification)				
WS/2045/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	29/04/2021	n/a		
WS/2027	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2 & 6.6. of the SmPC in order to include an improved method of administration and handling of the capsules, respectively. This update is based on post-marketing experience. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to correct the name of the local representative in Portugal. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/04/2021	11/10/2021	SmPC and PL	The MAH submitted with this variation an update of the Summary of Product Characteristics (SmPC) based on post-marketing experience. As a result, section "4.2. Posology and method of administration" includes a general recommendation that the capsule should not be opened or crushed and section "6.6. Special precautions for disposal and other handling" a statement that in the event of coming in contact with the content of the capsule, hands should be washed off immediately with plenty of water. For more information, please refer to the Summary of Product Characteristics.

IG/1374/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.z - Container closure system of the AS - Other variation 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.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.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.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same	08/04/2021	n/a		

	pharmaceutical group as the currently approved manufacturer				
II/0038	Update of sections 4.4 and 4.8 of the SmPC in order to add nephrotic range proteinuria to the list of adverse drug reactions (ADRs) with frequency Common, following the quarterly signal detection in EudraVigilance/EVDAS and based on MAH assessment of safety data retrieved from all completed ICTs conducted with nintedanib and the MAH Global Drug Safety System (GDSS); 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	11/02/2021	11/10/2021	SmPC and PL	Very few cases of nephrotic range proteinuria have been reported post marketing. Histological findings in individual cases were consistent with glomerular microangiopathy with or without renal thrombi. Reversal of symptoms has been observed after Vargatef was discontinued. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome. For more information, please refer to the Summary of Product Characteristics.
II/0035/G	This was an application for a group of variations. Update of sections 4.5, 4.6 and 5.2 of the SmPC to reflect the results of study 1199-0340 conducted in female patients with Systemic Sclerosis associated Interstitial Lung disease (SSc-ILD), to investigate a potential interaction between nintedanib and the oral contraceptive Microgynon, a combination of ethynilestradiol and levonorgestrel. Update of section 4.6 of the SmPC to reflect that patients receiving Vargatef treatment should use highly effective contraceptive methods. The MAH took the opportunity of this variation to implement the QRD template version 10.1 and introduce minor editorial changes to the labelling.	28/01/2021	11/10/2021	SmPC, Annex II, Labelling and PL	In a dedicated pharmacokinetic study, female patients with SSc-ILD received a single dose of a combination of 30 µg ethinylestradiol and 150 µg levonorgestrel before and after twice daily dosing of 150 mg nintedanib for at least 10 days. The adjusted geometric mean ratios (90% confidence interval (CI)) were 117% (108% – 127%; Cmax) and 101% (93% – 111%; AUC0–tz) for ethinylestradiol and 101% (90% – 113%; Cmax) and 96% (91% – 102%; AUC0–tz) for levonorgestrel, respectively (n=15), indicating that co-administration of nintedanib has no relevant effect on the plasma exposure of ethinylestradiol and levonorgestrel. However the efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhoea or other conditions where the absorption may be affected. Women taking oral hormonal contraceptives

	The Package Leaflet is updated accordingly. The RMP version 9.0 has also been submitted reflecting the consequential changes to the submission of study 1199-0340 and other changes requested by the PRAC. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				experiencing these conditions should be advised to use an alternative highly effective contraceptive measure. For more information, please refer to the Summary of Product Characteristics.
II/0037	Submission of the final report from study LUME BioNIS listed as an obligation in the Annex II of the Product Information. This is a non-interventional study in patients eligible for treatment with Vargatef to explore whether genetic or genomic markers (alone or combined with clinical covariates) could be used to predict overall survival. The Annex II and the RMP version 8.0 are updated accordingly. 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	14/01/2021	11/10/2021	Annex II	

IG/1293/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.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	16/10/2020	11/10/2021	Annex II and PL	
PSUSA/10318 /201910	Periodic Safety Update EU Single assessment - nintedanib (oncology indications)	28/05/2020	23/07/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10318/201910.
IG/1258	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	18/06/2020	n/a		
IG/1215/G	This was an application for a group of variations. 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	11/03/2020	n/a		

	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				
WS/1722	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to add alopecia with a frequency uncommon for Ofev and very common for Vargatef; and headache with a common frequency for both Ofev and Vargatef as new adverse drug reactions based on an overall assessment of the safety data for the nintedanib products. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to include the latest renewal date in the Vargatef SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/12/2019	23/07/2020	SmPC and PL	
IA/0029	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	21/11/2019	n/a		
IAIN/0027	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	27/09/2019	23/07/2020	SmPC and PL	
R/0025	Renewal of the marketing authorisation.	27/06/2019	26/08/2019	SmPC, Labelling and	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of

				PL	Vargatef in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10318 /201810	Periodic Safety Update EU Single assessment - nintedanib (oncology indications)	29/05/2019	31/07/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10318/201810.
IB/0024	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/02/2019	31/07/2019	Annex II	
IA/0023	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)	05/12/2018	n/a		
IB/0022	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	20/11/2018	n/a		
II/0021	Update of section 4.8 of the SmPC in order to add 'pruritus' as a new adverse drug reaction with a frequency 'common' following a routine review of post-marketing data. 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	26/07/2018	31/07/2019	SmPC and PL	Based on a routine periodic review of post-marketing data, the frequency of pruritus in patients treated with nintedanib in combination with docetaxel for the treatment of non-small cell lung cancer (NSCLC) was comparable to patients treated with docetaxel alone. In total 9 reports of a non-serious pruritus event were identified in the post-marketing and compassionate use setting. As it cannot be ruled out that there is a relationship between the use of nintedanib and the observed adverse drug reaction based on data from the more extensive use of nintedanib in the idiopathic pulmonary fibrosis (IPF) indication, 'pruritus' is added as a new adverse drug reaction in section 4.8 of the SmPC with

					a frequency 'common'.
PSUSA/10318 /201710	Periodic Safety Update EU Single assessment - nintedanib (oncology indications)	31/05/2018	23/07/2018	SmPC and PL	Please refer to VARGATEF PSUSA-00010318-201710 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
WS/1307	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC for Ofev and Vargatef to amend the current warning on drug induced liver injury based one case of sever liver injury with fatal outcome reported for Ofev during the post-marketing phase. In addition section 4.4 of the Ofev SmPC is updated to include when the majority of the hepatic events occurred and on the need for hepatic transaminases and bilirubin levels to be measured at regular intervals during the first 3 months of treatment. Section 4.8 of the Vargatef SmPC is also updated to include in the summary of the safety profile that the safety data is also based on post-marketing data. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to update the contact details of the Maltese local representative and to make some corrections to the Bulgarian, Estonian, Icelandic, Latvian and Maltese translations for Ofev and Bulgarian, Estonian, Latvian and Maltese translations for Vargatef. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	26/04/2018	23/07/2018	SmPC and PL	Cases of drug-induced liver injury have been observed with nintedanib treatment, including severe liver injury with fatal outcome. The majority of hepatic events occur within the first three months of treatment. Therefore, hepatic transaminase and bilirubin levels should be investigated before treatment initiation and during the first month of treatment with Ofev. Patients should then be monitored at regular intervals during the subsequent two months of treatment and periodically thereafter, e.g. at each patient visit or as clinically indicated. Elevations of liver enzymes (ALT, AST, ALKP, gamma-glutamyl-transferase (GGT)) and bilirubin were reversible upon dose reduction or interruption in the majority of cases. If transaminase (AST or ALT) elevations > 3x ULN are measured, dose reduction or interruption of the therapy with Ofev is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with Ofev may be resumed at the full dose (150 mg twice daily) or reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose. If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with Ofev should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

	data				
II/0018	Update of section 4.4 of the SmPC to amend the current warning on hepatic function to include that drug liver induced injury was associated with nintendanib administration, to include low body weight, Asian origin, female sex and age as factors of increased risk of liver enzymes elevations, update of section 4.8 of the SmPC to add 'drug-induced liver injury' (DILI) as new ADR with an 'uncommon' frequency and update of section 5.2 of the SmPC to amend the current information related to the mean exposure to nintedanib by race, based on a review of clinical trials and post-marketing data on DILI and on the exposure safety relationship between nintedanib plasma exposure and liver enzyme elevations, as requested by the PRAC as part of PSUSA/00010318/201611. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make some minor changes to section 4.4 and 4.8 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	23/07/2018	SmPC and PL	Based on a review of clinical trials and post-marketing data on drug liver injury (DILI) and on the exposure safety relationship between nintedanib plasma exposure and liver enzyme elevations, the new adverse drug reaction 'DILI' was included in section 4.8 of the SmPC with an 'uncommon' frequency. Administration of nintedanib was associated with an elevation of liver enzymes (ALT, AST, ALKP, gamma-glutamyltransferase (GGT)), bilirubin and drug-induced liver injury. These increases were generally reversible upon dose reduction or interruption in the majority of cases. Patients with low body weight (< 65 kg), female and Asian patients have a higher risk of elevations in liver enzymes. Nintedanib exposure increased linearly with patient age, which may also result in a higher risk of developing liver enzyme elevations. Close monitoring is recommended in patients with these risk factors. The population mean exposure to nintedanib was 33 - 50% higher in Chinese, Taiwanese, and Indian patients and 16% higher in Japanese patients while it was 16 - 22% lower in Koreans compared to Caucasians (body weight corrected). Data from Black individuals were very limited but in the same range as for Caucasians.
II/0017	Update of section 4.8 of the SmPC in order to add 'weight decreased' as a new adverse drug reaction based on a safety review of clinical trials and post-marketing data. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement a	14/09/2017	23/07/2018	SmPC and PL	

	minor correction in the English product information, minor corrections to the Croatian, Danish, Dutch and Finnish translations and to bring section 4 of the Package Leaflet in line with QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10318 /201611	Periodic Safety Update EU Single assessment - nintedanib (oncology indications)	22/06/2017	14/08/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10318/201611.
IG/0801	B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation	11/05/2017	n/a		
PSUSA/10318 /201605	Periodic Safety Update EU Single assessment - nintedanib (oncology indications)	15/12/2016	23/02/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10318/201605.
WS/1090/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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)	09/02/2017	n/a		

WS/0998	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	23/02/2017	SmPC, Labelling and PL	
II/0009	Update of sections 4.2 and 4.4 of the SmPC to amend the current wording on hepatic impairment and to reflect the limited experience in patients with moderate hepatic impairment (Child Pugh B) based on the final clinical study report for study 1199.120: an open label, dose escalation phase I study to evaluate the safety and tolerability of continuous twice-daily oral treatment of nintedanib in Japanese patients with hepatocellular carcinoma. This submission fulfils MEA 003. The RMP has been amended accordingly. In addition the MAH took the opportunity to update the RMP with the required updates requested as part of EMEA/H/C/WS0766. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/09/2016	23/02/2017	SmPC	Results from study 1199.120 showed that based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A; see sections 4.2 and 5.2). Limited safety data are available in 9 patients with hepatocellular carcinoma and moderate hepatic impairment classified as Child Pugh B. Although no unexpected safety findings were reported in these patients, the data are insufficient to support a recommendation for treatment of patients with moderate hepatic impairment. The efficacy of nintedanib has not been investigated in patients with moderate hepatic impairment (Child Pugh B). These findings are reflected under section 4.4 of the SmPC. Section 4.2 is also amended to reflect that limited safety data available from 9 patients with moderate hepatic impairment (Child Pugh B) are insufficient to characterize this population. The RMP has been amended accordingly to reflect the information.
PSUSA/10318 /201511	Periodic Safety Update EU Single assessment - nintedanib (oncology indications)	23/06/2016	18/08/2016	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10318/201511.
IA/0012	A.5.b - Administrative change - Change in the name	03/08/2016	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
IA/0010/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.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) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	08/07/2016	n/a		
WS/0766	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to include further information related to patients with hepatic impairment based on the CSRs for studies 1199.37, 1199.39 and 1199.200. In addition, the MAH took the opportunity to make editorial changes in the SmPC, labelling and Package	28/01/2016	31/03/2016	SmPC, Labelling and PL	In a dedicated single dose phase I study and compared to healthy subjects, exposure to nintedanib based on Cmax and AUC was 2.2-fold higher in volunteers with mild hepatic impairment (Child Pugh A; 90% CI 1.3 – 3.7 for Cmax and 1.2 – 3.8 for AUC, respectively). In volunteers with moderate hepatic impairment (Child Pugh B), exposure was 7.6-fold higher based on Cmax (90% CI 4.4 – 13.2) and 8.7-fold higher (90% CI 5.7 – 13.1) based on AUC, respectively, compared to healthy volunteers. Subjects with severe hepatic impairment (Child Pugh C) have not been

	Leaflet, to merge the SmPCs for the 100 mg and 150 mg strengths and to update the contact details of the local representative in Portugal in the Package Leaflet. The provision of the CSR of study 1199.200 addresses the post-authorisation measure MEA 001. A revised RMP version was agreed during the procedure; RMP version 2.1 for OFEV and RMP version 3.1 for Vargatef. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				studied. Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A). However, no adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A). The safety and efficacy of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Vargatef is not recommended.
IB/0007	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	06/01/2016	n/a		
PSUSA/10318 /201505	Periodic Safety Update EU Single assessment - nintedanib (oncology indications)	03/12/2015	n/a		PRAC Recommendation - maintenance
IB/0004	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	13/05/2015	n/a		
IB/0003/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 C.I.11.z - Introduction of, or change(s) to, the	24/04/2015	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IA/0002	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	10/04/2015	31/03/2016	SmPC	
II/0001	Submission of the final non-clinical trial report for study PK140T (in vitro evaluation of the interaction of nintedanib with human OAT transporters) in order to fulfil a post-authorisation measure (MEA) included as additional activity in the RMP. A revised RMP version 2.0 was provided as part of this application. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		This variation did not lead to any changes in the product information.