Ofev

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
IB/0060/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	27/02/2024		SmPC and PL	

[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).

	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 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				

PSUSA/10319 /202304	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	30/11/2023	n/a		PRAC Recommendation - maintenance
IB/0056/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	09/10/2023	n/a		
X/0052/G	This was an application for a group of variations. Update of sections 4.2, 4.8, 5.1, 5.2 of the SmPC based on results of the trial 1199-0337 (InPedILD) in paediatric patients with clinically significant interstitial lung disease (ILD) and results of a food compatibility study conducted during paediatric development. The Package leaflet is updated accordingly. Consequently, the RMP is updated. Minor QRD changes are also introduced in the labelling. The variation leads to amendments to the Summary of Product Characteristics, labelling and Package	22/06/2023	28/07/2023	SmPC, Labelling and PL	The SmPC is updated based on results of the completed paediatric trial InPedILD and results from a food compatibility study performed in paediatric patients. A total of 39 patients aged 6 to 17 years were treated in a randomised, double-blind, placebo-controlled trial of 24 weeks duration (InPEdILD), followed by open label treatment with nintedanib of variable duration. The InPedILD trial enrolled children and adolescents aged 6 to 17 years with clinically significant fibrosing ILD and FVC of at least 25% predicted. The most frequent single underlying ILD diagnoses were 'surfactant protein deficiency' (nintedanib: 26.9%, placebo: 38.5%), 'systemic sclerosis' (nintedanib: 15.4%, placebo: 23.1%), and

	Leaflet and to the Risk Management Plan (RMP). The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0438/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				'toxic/radiation/drug-induced pneumonitis' (nintedanib: 11.5%, placebo 7.7%). Chronic hypersensitivity pneumonitis was reported for 2 patients (nintedanib: 7.7%). The use of standard of care as deemed clinically indicated by the treating physician was allowed. There was no primary efficacy endpoints in the study. Secondary endpoint for lung function was the change in Forced Vital Capacity (FVC) % predicted from baseline at week 24 and week 52. The adjusted mean change from baseline at week 24 in FVC % predicted was 0.31 (95% CI 2.36, 2.98) in the nintedanib group, and 0.89 (95% CI 4.61, 2.82) in the placebo group, with an adjusted mean (95% CI) difference in FVC % predicted of 1.21 (95% CI 3.40, 5.81) in favour of nintedanib. At week 52, the adjusted mean of the difference in change from baseline in FVC % predicted between treatment groups was 1.77 (95% CI 4.70, 8.25). For the FVC % predicted endpoint and a number of other exploratory efficacy endpoints, high variability in response to treatment with nintedanib was observed amongst paediatric patients. Consistent with the safety profile seen in adult patients with IPF, other chronic fibrosing ILDs with progressive phenotype and SSc-ILD, the most frequently reported adverse reactions with nintedanib during placebo-controlled period were diarrhoea (38.5%), vomiting (26.9%), nausea (19.2%), abdominal pain (19.2%), and headache (11.5%). Hepatobiliary disorders reported with nintedanib during placebo-controlled period were liver injury (3.8 %) and increased liver function test (3.8 %). Due to limited data, it is uncertain if the risk for drug-induced liver injury is similar in children as compared to adults.

					Based on preclinical findings, bone, growth and teeth development were monitored as potential risks in the paediatric clinical trial. The potential impact on growth and tooth development is unknown, thus, an update of the RMP was introduced accordingly. Long term safety data in paediatric patients are not available. There are uncertainties on the potential impact on growth, tooth development, puberty, and the risk of liver injury. For more information, please refer to the Summary of Product Characteristics. The PL has been updated accordingly.
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-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)	25/07/2023	n/a		

PSUSA/10319 /202210	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	12/05/2023	n/a		PRAC Recommendation - maintenance
PSUSA/10319 /202204	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	01/12/2022	n/a		PRAC Recommendation - maintenance
PSUSA/10319 /202110	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	10/06/2022	n/a		PRAC Recommendation - maintenance
IG/1505/G	This was an application for a group of variations. B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure 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.a - Change in test procedure for an excipient - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites 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 A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	03/06/2022	n/a		

	changes to an approved test procedure				
II/0046	Update of the RMP to version 11.2 in order to fulfil a request made in the renewal (EMEA/H/C/003821/R/0025) to remove the following safety concerns (Modules SIV, SVII, SVIII; Parts III, V, VI; Appendices 4, 8) in line with GVP module V (Rev. 2): 1-Important identified risks: Diarrhoea, Liver enzyme and bilirubin elevations; 2-Important potential risks: Treatment of pregnant women and teratogenicity, Cardiac failure; 3-Missing information: Treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C), Treatment of Black patients, Treatment of patients with healing wounds, Treatment of patients with severe renal impairment or end-stage renal disease, Treatment of patients receiving full-dose therapeutic anticoagulation, and Treatment of breastfeeding women. 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	07/04/2022	n/a		The RMP is updated to version 11.1 to remove the following risks since no additional risk minimisation measures nor additional pharmacovigilance activities are proposed: 1. Important identified risks: Diarrhoea, Liver enzyme and bilirubin elevations; 2. Important potential risks: Treatment of pregnant women and teratogenicity, Cardiac failure; 3. Missing information: Treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C), Treatment of Black patients, Treatment of patients with healing wounds, Treatment of patients with severe renal impairment or end-stage renal disease, Treatment of patients receiving full-dose therapeutic anticoagulation, and Treatment of breastfeeding women. Nonetheless, it was concluded that the following risks, and previously implemented Pharmacovigilance activities (e.g. specific FU questionnaire) and/or risk minimisation measures, should remain in the RMP: 1. Important identified risks: DILI, Bleeding, and Myocardial infarction. 2. Important potential risks: Venous thromboembolism, Arterial thromboembolism excluding myocardial infarction, Perforation and Hepatic failure. 3. Missing information: Treatment of SSc-ILD patients with pulmonary hypertension.
IB/0049/G	This was an application for a group of variations. B.II.c.3.z - Change in source of an excipient or	21/02/2022	n/a		

	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				
IG/1463	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	18/11/2021	31/10/2022	SmPC, Labelling and PL	
PSUSA/10319 /202104	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	28/10/2021	n/a		PRAC Recommendation - maintenance
PSUSA/10319 /202010	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	24/06/2021	18/08/2021	SmPC and PL	Please refer to OFEV EMEA/H/C/PSUSA/00010319/202010 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0040	Update of sections 4.8. and 4.4. of the SmPC in order to add "nephrotic range proteinuria" as a new adverse drug reaction with a frequency of "uncommon" for "Idiopathic pulmonary fibrosis (IPF)" and "Other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype" and with a frequency of "not known" for "Systemic sclerosis associated interstitial lung disease (SSc-ILD)"and its relevant warning, respectively; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make	06/05/2021	18/08/2021	SmPC, Annex II and PL	The MAH submitted with this variation an update of the Summary of Product Characteristics (SmPC) based on cases of proteinuria identified in clinical trials and in the post-marketing setting. As a result, sections " 4.4. Special warnings and precautions for use" and "4.8. Undesirable effects" have been updated accordingly. Section 4.4. includes a warning for "Nephrotic range proteinuria" to indicate that very few cases of nephrotic range proteinuria with or without renal function impairment have been reported post-marketing. Histological findings in individual cases were consistent with glomerular microangiopathy with or without renal thrombi. Reversal of the symptoms

	minor corrections and editorial changes (correction of frequency category for renal failure in section 4.8 of the SmPC, correction of a typo of non-safety relevant information in section 5.1. of the SmPC and correction of typos in Annex II) in the EN PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				has been observed after Ofev was discontinued, with residual proteinuria in some cases. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome. Section 4.8. includes the new adverse reaction for proteinuria with a frequency of "uncommon" for "Idiopathic pulmonary fibrosis (IPF)" and "Other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype" and with a frequency of "not known" for "Systemic sclerosis associated interstitial lung disease (SSc-ILD)". A paragraph on clinical trial experience has also been added to align with the description of other selected adverse reactions in the SmPC.
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	09/04/2021	18/08/2021	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

	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				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	08/04/2021	n/a		

	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 pharmaceutical group as the currently approved manufacturer				
PSUSA/10319 /202004	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	12/11/2020	07/01/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10319/202004.
II/0034	Update of section 5.1 of SmPC to include results of a double-blind, randomised, parallel-group trial to evaluate the efficacy and safety of Ofev co-administered with oral sildenafil, compared to treatment with Ofev alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment (INSTAGE clinical trial). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/12/2020	18/08/2021	SmPC	The MAH submitted clinical data from the INSTAGE clinical trial aimed to evaluate the efficacy and safety of Ofev co-administered with oral sildenafil, compared to treatment with Ofev alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment. For IPF patients with advanced lung function impairment (DLCO ≤ 35% predicted) the primary endpoint result showed a reduction of St Georges Respiratory Questionnaire (SGRQ) total score by -0.77 units at week W12, based on adjusted mean change from baseline. A post hoc comparison also demonstrated that the decline in FVC in these patients was consistent with the decline in FVC in patients with less advanced disease and treated with Ofev in the INPULSIS phase III trials. Furthermore, the safety and tolerability

					profile of Ofev in IPF patients with advanced lung function impairment was also consistent with that seen in the INPULSIS phase III trials. For more information, please refer to the Summary of Product Characteristics.
II/0038	Update of sections 4.5, 4.6 and 5.2 of the SmPC in order to add drug-drug interaction information with the oral contraceptive Microgynon, a combination of ethynilestradiol and levonorgestrel based on final) based on final results from clinical study Nº1199-0340. This was a phase I, open-label, 2-period cross-over, fixed-sequence design trial, investigated the effect of multiple oral doses of nintedanib on the single dose kinetics of a combination of ethinylestradiol and levonorgestrel (Microgynon). The Package Leaflet is updated accordingly. The RMP is likewise updated to version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/11/2020	18/08/2021	SmPC and PL	The MAH submitted clinical data from a new study (Nº 1199-0340) aimed to investigate the effect of multiple oral doses of nintedanib on the single-dose pharmacokinetics of a combination of ethinylestradiol and levonorgestrel (Microgynon). Results demonstrated that co-administration of nintedanib with oral hormonal contraceptives did not alter the pharmacokinetics of oral hormonal contraceptives to a relevant extent. In addition, women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Ofev and to use highly effective contraceptive methods at initiation of, during and at least 3 months after the last dose of Ofev. Nintedanib did not relevantly affect the plasma exposure of ethinylestradiol and levonorgestrel. It was also found that 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 experiencing these conditions should be advised to use an alternative highly effective contraceptive measure. Findings on the concomitant treatment with oral hormonal contraceptives indicated that co-administration of nintedanib had no relevant effect on the plasma exposure of ethinylestradiol and levonorgestrel.
II/0033	Update of SmPC Sections 5.1. to include additional	06/11/2020	07/01/2021	SmPC	Clinical information from an open-label extension trial

	clinical information from an open-label extension trial 1199.33 (INPULSIS-ON) of the pivotal phase III, randomised, double-blind, placebo-controlled studies with identical design (INPULSIS-1 (1199.32) and INPULSIS-2 (1199.34)). This trial provides safety and efficacy data up to 192 weeks. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				1199.33 (INPULSIS-ON) of the pivotal phase III, randomised, double-blind, placebo-controlled studies with identical design (INPULSIS-1 (1199.32) and INPULSIS-2 (1199.34)) has been submitted. This trial provides safety and efficacy data up to 192 weeks. The exploratory efficacy endpoints included the annual rate of decline in FVC over 192 weeks which was −135.1 (5.8) mL/year in all patients treated. They were consistent with the annual rate of FVC decline in patients treated with Ofev in the INPULSIS phase III trials (−113.6 mL per year). The adverse event profile of Ofev in INPULSIS-ON was consistent to that in the INPULSIS phase III trials (INPULSIS-1 (1199.32) and INPULSIS-2 (1199.34)).
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	07/01/2021	Annex II and PL	
II/0027	Extension of Indication to include new indication for OFEV for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype based on the results of pharmacology studies and the double-blind, randomised, placebo-controlled phase III trial (INBUILD). Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC	28/05/2020	13/07/2020	SmPC, Annex II and PL	Please refer to Scientific Discussion: Ofev EMEA/H/C/003821/II/0027

	are updated in order to reflect the use of Ofev in the new indication. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor formatting changes in the PI. Furthermore, the PI is brought in line with the latest QRD template version 10.1. The RMP version 9.1 has also been adopted. The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
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		
PSUSA/10319 /201910	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	14/05/2020	n/a		PRAC Recommendation - maintenance
II/0026	Extension of Indication to include a new indication for OFEV for the treatment of Systemic Sclerosis associated Interstitial Lung Disease. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local	27/02/2020	17/04/2020	SmPC and PL	Please refer to Scientific Discussion OFEV EMEA/H/C/3821/II/0026.

	representatives in the Package Leaflet. The MAH takes this opportunity to also introduce minor linguistic corrections to the Annexes for France and Sweden. The RMP version 7.2 has also been adopted. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
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 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	11/03/2020	n/a		
WS/1722	This was an application for a variation following a	12/12/2019	17/04/2020	SmPC and PL	

	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				
IA/0030	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/0028	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	27/09/2019	17/04/2020	SmPC and PL	
R/0025	Renewal of the marketing authorisation.	25/07/2019	23/09/2019	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Ofev in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. The following annexes have been amended with minor formatting changes and removal of the black triangle symbol on additional

					monitoring: I and IIIB.
PSUSA/10319 /201810	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	29/05/2019	25/07/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10319/201810.
IB/0022	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/12/2018	n/a		
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		
II/0021	Update of section 4.8 of the SmPC in order to include 'myocardial infarction' as a new adverse drug reaction with a frequency 'uncommon' in order to fulfil LEG 004.1, following the assessment of PSUSA/00010319/201704. The Package Leaflet is updated accordingly. The RMP version 6.3 (in revision 2 of the template) is also updated accordingly. 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	31/10/2018	25/07/2019	SmPC and PL	
PSUSA/10319 /201710	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	31/05/2018	26/07/2018	SmPC and PL	Please refer to Ofev-EMEA/H/C/PSUSA/00010319/201710 EPAR: Scientific conclusions and grounds recommending

					the variation to the terms of the marketing authorisation
II/0018/G	This was an application for a group of variations. Update of section 4.4 in order to amend the current warning on co-administration with pirfenidone and update of section 5.1 to include the results of study 1199.222, a phase IV, 12 week, open label, randomised, parallel group study to evaluate the safety, tolerability and pharmacokinetics of oral nintedanib in combination with oral pirfenidone in comparison with nintedanib alone in patients with idiopathic pulmonary disease (IPF). The Package Leaflet is updated accordingly. Update of section 5.2 of the SmPC in order to include the results of study 1199.229, a phase IV, open label, multi-dose, 2 groups study to investigate the drug-drug interaction between nintedanib anfd pirfenidone in patients with IPF, a category 3 study in the RMP. The RMP version 5.1 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement some corrections to the French and Swedish translations. 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	17/05/2018	26/07/2018	SmPC	In a dedicated pharmacokinetic study, concomitant treatment of nintedanib with pirfenidone was investigated in patients with idiopathic pulmonary fibrosis (IPF). Based on these results, there is no evidence of a relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone when administered in combination. Additional data from the phase IV INJOURNEY trial with Ofev 150 mg twice daily and add-on pirfenidone for 12 weeks were provided. In view of the limited number of patients, this study detected only the most frequent adverse events and showed an increase in gastrointestinal adverse events and a trend toward increased hepatic adverse events. Given the similarity in safety profiles for both medicinal products, additive adverse events, including gastrointestinal and hepatic adverse events, may be expected. The benefit-risk balance of concomitant treatment with pirfenidone has not been established.

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 data	26/04/2018	26/07/2018	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.
PSUSA/10319 /201704	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	26/10/2017	n/a		PRAC Recommendation - maintenance

II/0016	Update of section 4.4 of the SmPC to amend the current warning on the hepatic function 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 revised the frequency of the ADR 'drug-induced liver injury' (DILI) from 'not known' to 'uncommon' 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. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make a small correction in section 5.2 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2017	26/07/2018	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 frequency of the adverse drug reaction 'DILI' was update from 'not known' to 'uncommon'. Patients with low body weight (< 65 kg), Asian and female patients have a higher risk of elevations of 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.
PSUSA/10319 /201610	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	18/05/2017	19/07/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10319/201610.
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		

IB/0014	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	02/05/2017	n/a		
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		
PSUSA/10319 /201604	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	10/11/2016	09/01/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10319/201604.
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	09/01/2017	SmPC, Labelling and PL	
II/0006	Update of sections 4.2 and 4.4 of the SmPC in order to revise dose recommendations for patients with mild hepatic impairment, based on PK/PD modelling data.	21/07/2016	02/09/2016	SmPC and Annex II	The marketing authorisation holder for Ofev (indicated in the treatment for fibrosis of the lungs) recommends that a lower dose (100 mg instead of 150 mg) should be used in patients with mild liver impairment as this reduction may

	In addition, the marketing authorisation holder took the opportunity to bring the Annex II in line with the latest QRD template version 10. Furthermore, the MAH introduced minor linguistic corrections to the Italian product information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				reduce the frequency of unwanted effects while still providing sufficiently high drug levels to maintain effectiveness.
IA/0010	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)	03/08/2016	n/a		
IB/0009	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/07/2016	n/a		
PSUSA/10319 /201510	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	26/05/2016	22/07/2016	SmPC and PL	Please refer to Ofev-PSUSA 10319-201510 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IA/0007/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	08/07/2016	n/a		

	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				
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 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	28/01/2016	22/07/2016	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 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

	new quality, preclinical, clinical or pharmacovigilance data				impairment with Vargatef is not recommended.
PSUSA/10319 /201504	Periodic Safety Update EU Single assessment - nintedanib (respiratory indication)	19/11/2015	22/01/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10319/201504.
IB/0004	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	06/01/2016	n/a		
IB/0001	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	13/05/2015	n/a		