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
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	31/10/2018		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).

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	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				
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	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.

	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				
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	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

	new quality, preclinical, clinical or pharmacovigilance data				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	11/05/2017	n/a		

	starting material/reagent/intermediate for AS - Introduction of a new site of micronisation				
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	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

	hepatic impairment, based on PK/PD modelling data. 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				dose (100 mg instead of 150 mg) should be used in patients with mild liver impairment as this reduction may 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	08/07/2016	n/a		

	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				
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 new quality, preclinical, clinical or pharmacovigilance	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 impairment

	data				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		