PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

PART VI.1 SUMMARY OF RISK MANAGEMENT PLAN FOR OFEV (NINTEDANIB)

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

Ofev's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ofev should be used.

This summary of the RMP for Ofev should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ofev's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Ofev is authorised for treatment if idiopathic pulmonary fibrosis (see SmPC for the full indication). It contains nintedanib as the active substance and it is given by oral administration.

Further information about the evaluation of Ofev's benefits can be found in Ofev's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Ofev is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ofev are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ofev. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	Diarrhoea
	Liver enzyme and bilirubin elevations including DILI
	Bleeding
	Myocardial infarction
Important potential risks	Venous thromboembolism
	Arterial thromboembolism excluding myocardial infarction
	Perforation
	Hepatic failure
	Treatment of pregnant women and teratogenicity
	Cardiac failure
	QT prolongation
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
	Interaction of Ofev with hormonal contraceptives
	Treatment of breastfeeding women

II.B Summary of important risks

PVI.Table 1 Important identified risks

Diarrhoea	
Evidence for linking the risk to the medicine	In the clinical development, diarrhoea was the most frequently reported AE associated with the use of Ofev (61.6% in the Ofev arm vs. 18.4% in the placebo arm). Furthermore, diarrhoea is the most frequently reported ADR in the post-marketing setting.
Risk factors and risk groups	Subgroup analyses showed comparable results between treatment groups. No clinically meaningful difference in frequency of diarrhoea was observed with regard to gender, race, age, renal impairment, or smoker status.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Liver enzyme and bilirubin elevations including DILI	
Evidence for linking the risk to the medicine	In clinical trials, liver enzyme and bilirubin elevation AEs occurred more frequently in patients treated with Ofev than in those treated with placebo. Furthermore, liver enzyme elevations are among the most common reported adverse events in the post-marketing setting whereas reports of DILI are uncommon.
Risk factors and risk groups	A study based on the Drug Induced Liver Injury Network (DILIN) in the US assessed the characteristics of DILI patients aged 65 years and above. In this cohort (n=149), 60% of the patients were female and 85% were White. The highest

	proportion of patients (58%) took at least 6 medications. Among the DILI patients, antimicrobial agents were the most common class of causative drugs with 57.7%. Subgroup analyses suggest that the subgroup of Asian patients and the subgroup of female patients treated with Ofev may be at higher risk of 'liver related investigation' than White patients and male patients, respectively. Based on PK population analysis, 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.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Bleeding	
Evidence for linking the risk to the medicine	In the INPULSIS trials with Ofev, the frequency of patients who experienced bleeding AEs was slightly higher in the Ofev arm (10.3%) than in the placebo arm (7.8%). Non-serious epistaxis was the most frequent bleeding event in clinical trials. In the post-marketing period, non-serious and serious bleeding events have been reported (including patients with or without anticoagulant therapy or other drugs that could cause bleeding).
Risk factors and risk groups	Patients at known risk for bleeding including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulant treatment were not included in the INPULSIS studies. Subgroup analyses showed similar results between treatment groups. No clinically meaningful difference in frequency of bleeding was observed with regard to gender, race, age, renal impairment,

	or smoker status.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Myocardial infarction	
Evidence for linking the risk to the medicine	In clinical trials, while AEs reflecting ischaemic heart disease were balanced between the nintedanib and placebo groups, a higher percentage of patients experienced myocardial infarction in the nintedanib group (1.7%) compared to the placebo group (0.5%).
Risk factors and risk groups	Patients with a recent history of myocardial infarction or stroke were excluded from the INPULSIS trials. Based on the low number of patients affected in clinical trials, no clinically meaningful difference in frequency of myocardial infarction was observed with regard to gender, race, age, renal impairment, or smoker status. Independently of treatment, there is an increased risk within the IPF population for cardiovascular events including coronary artery disease, myocardial infarction, and stroke based on epidemiological data.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None

PVI.Table 2 Important potential risks

Venous thromboembolism	
Evidence for linking the risk to the medicine	In the INPULSIS trials with Ofev, the frequency of patients with venous thromboembolism was similar in both arms (1.2% placebo, 1.1% Ofev). Events comprised predominantly pulmonary embolism and deep vein thrombosis. There was no evidence from the clinical trial programme with Ofev to suggest that venous thromboembolism is an important identified risk in patients with IPF. Nevertheless, the risk of venous thromboembolism resulting from the mode of action of Ofev cannot be entirely ruled out, and so venous thromboembolism is considered an important potential risk.
Risk factors and risk groups	Due to the small numbers of patients who experienced venous thromboembolism in randomised, placebo-controlled clinical trials, the subgroup assessment is not considered meaningful. Independently of treatment, a number of major risk factors for venous thromboembolism/pulmonary embolism have been identified: old age (>65 years), long-haul travel, thrombophilia, obesity, cigarette smoking, hypertension, metabolic syndrome, immobilisation, cancer, and acute medical illness, among others. Studies reported higher incidence rates of venous thromboembolism/pulmonary embolism for IPF patients compared to controls. This is probably explained by the fact that IPF patients have advanced age and frequently 1 or more additional risk factors for thromboembolism. Also, acute medical illness, such as pneumonia, has also been described as a risk factor for pulmonary embolism.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None

Arterial thromboembolism excluding myocardial infarction	
Evidence for linking the risk to the medicine	In INPULSIS clinical trials, arterial thromboembolism was reported at slightly higher rate in the nintedanib group (2.5%) compared to the placebo group (0.7%). The most frequently reported events were myocardial infarction, as described among important identified risks above.
Risk factors and risk groups	Based on the low number of patients affected, no clinically meaningful difference in frequency of arterial thromboembolism was observed with regard to gender, race, age, renal impairment, or smoker status.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Perforation	
Evidence for linking the risk to the medicine	In the INPULSIS trials, the frequency of patients with gastrointestinal perforation was very low: 0% placebo, 0.3% Ofev (involving 2 patients). gastrointestinal perforations are known to occur in cancer patients treated with tyrosine kinase inhibitors, and as such were defined as important potential risk.
Risk factors and risk groups	Due to the small numbers of patients who experienced perforation in randomised, placebo-controlled clinical trials, the subgroup assessment is not considered meaningful. Independently of treatment, a number of risk factors for gastrointestinal perforation such as preceding abdominal surgery and use of corticosteroids or non-steroid anti-inflammatory drugs have been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Restricted medical prescription

	Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Hepatic failure	
Evidence for linking the risk to the medicine	In the INPULSIS clinical trials, hepatic failure was not reported. Liver enzyme and bilirubin elevations including DILI is an important identified risk with Ofev; therefore, the potential for further sequelae of liver abnormality is warranted for monitoring 'hepatic failure' as a potential risk.
Risk factors and risk groups	Based on the low number of patients affected, no clinically meaningful difference in frequency of hepatic failure was observed with regard to gender, race, age, renal impairment, or smoker status.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Treatment of pregnant women and teratogenicity	
Evidence for linking the risk to the medicine	Angiogenesis is critical to foetal development. Following administration of nintedanib to rats, the inhibition of angiogenesis resulted in absorption of foetuses and increased incidence of malformations. These effects occurred at dose levels resulting in plasma drug concentrations comparable to, or lower than, those reached in humans during treatment with Ofev. Beside the potential teratogenic effect, side effects of Ofev such as gastrointestinal AEs may affect pregnant women and may have consequences for the unborn child.
Risk factors and risk groups	Women of childbearing potential are at risk of becoming pregnant if they do not use effective contraception, or failure of contraception occurs.
Risk minimisation measures	Routine risk minimisation measures:

	SmPC section 4.6 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Cardiac failure	
Evidence for linking the risk to the medicine	Some tyrosine kinase inhibitors (e.g. sorafenib, sunitinib) are associated with undesirable effects such as congestive cardiac failure or decrease in left ventricular ejection fraction. Other tyrosine kinase inhibitors (e.g. axitinib) do not present with such effects. It is presently not possible to define a specific group of tyrosine kinase inhibitors which typically may be considered to bear an increased risk of impairing left ventricular function.
Risk factors and risk groups	Based on the low number of patients affected, no clinically meaningful difference in frequency of cardiac failure was observed with regard to gender, race, age, renal impairment, or smoker status.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
QT prolongation	
Evidence for linking the risk to the medicine	Non-clinical and clinical data do not show evidence that Ofev has an increased risk of QT prolongation as reported for some other tyrosine kinase inhibitors.
Risk factors and risk groups	Due to the small numbers of patients who experienced events that might point to QT prolongation in randomised, placebo-controlled clinical trials, the subgroup assessment is not considered meaningful.

	Risk factors for QT prolongation are female gender, low serum potassium, low serum magnesium, bradycardia, left ventricular hypertrophy, congestive heart failure, recent conversion from atrial fibrillation, a family history of long QT syndrome, and use of QT prolonging drugs.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None

PVI.Table 3 Missing information

Treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C)	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures None
Treatment of Black patients	
Risk minimisation measures	Routine risk minimisation measures: Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Treatment of patients with healing wounds	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2

	Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Treatment of patients with severe renal impairment or end-stage renal disease	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Treatment of patients receiving full-dose therapeutic anticoagulation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Interaction of Ofev with hormonal contraceptives	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.5 and 4.6 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF Additional risk minimisation measures: None
Treatment of breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF

	Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:
There are no studies which are conditions of the marketing authorisation or specific obligation of Ofev.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Ofev.

ABBREVIATIONS

AE	Adverse event
ADR	Adverse drug reaction
DILI	Drug-induced liver injury
EMA	European Medicines Agency
EPAR	European Public Assessment Report
IPF	Idiopathic pulmonary fibrosis
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics