OFEV (Nintedanib)
Weichkapseln
ZL-Nr.: 65330

Public Risk Management Plan (RMP) Summary

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Boehringer Ingelheim (Schweiz) GmbH
Hochbergerstrasse 60B
CH-4057 Basel
www.boehringer-ingelheim.ch

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Ofev is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of Ofev in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic.

Boehringer Ingelheim (Schweiz) GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ofev.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

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, how these risks can be minimised, 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 of idiopathic pulmonary fibrosis, for treatment of systemic sclerosis associated interstitial lung disease, and for treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (see SmPC for the full indications). 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 used. 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	Drug-induced liver injury (DILI)
	Bleeding
	Myocardial infarction
Important potential risks	Venous thromboembolism
	Arterial thromboembolism excluding myocardial infarction
	Perforation
	Hepatic failure
	Effect on bone development and growth if used off-label in paediatric patients <18 years-of-age
	Effect on teeth development if used off-label in paediatric patients <18 years-of-age
Missing information	Treatment of SSc-ILD patients with pulmonary hypertension

II.B Summary of important risks

Important identified risks

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	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%. Indication IPF: A broader analysis of 'liver related investigation' suggested 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. Indication SSc-ILD: A broader analysis of 'liver related investigation' indicated a higher frequency of 'liver related investigation' in female than male patients and in Asian than in White/Black patients. There was an increase in frequency with increasing age. No clinically meaningful difference in frequency of 'liver related investigation' between nintedanib and placebo was observed in the remaining subgroups. Indication PF-ILD: A broader analysis of 'liver related investigation' suggested that Asian, female, and patients with a low body weight (≤65 kg) may be at higher risk of 'liver related investigation'. No clinically meaningful differences were observed in the remaining subgroups.
Risk minimisation measures	Routine risk minimisation measures EU-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 the respective indications Additional risk minimisation measures None
Bleeding	
Evidence for linking the risk to the medicine	In the clinical trials, the frequency of patients who experienced bleeding AEs was slightly higher or similar in the Ofev treatment group than in the placebo group. Bleeding events were mostly not serious 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 studies. Subgroup analyses showed similar results between treatment groups. No clinically meaningful difference in frequency of bleeding was observed in the analysed subgroups. SSc may affect the blood vessels in the stomach, which predisposes patients with SSc to a higher risk of gastrointestinal bleeding than the general population.
Risk minimisation measures	Routine risk minimisation measures: EU-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 the respective indications Additional risk minimisation measures: None
Myocardial infarction	
Evidence for linking the risk to the medicine	In the IPF (INPULSIS) studies, 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%). In the SSc-ILD (SENSCIS) studies, no MI was reported in the Ofev group. In the PF-ILD study, the frequency of MI was the same between the nintedanib

	and the placebo group (0.9% each).
Risk factors and risk groups	Patients with a recent history of myocardial infarction or stroke were excluded from the trials. Based on the low number of patients affected in clinical trials, no clinically meaningful difference in frequency of myocardial infarction was observed in the analysed subgroups. Independently of treatment, there is an increased risk within the IPF/SSc/PF-ILD population for cardiovascular events including coronary artery disease, myocardial infarction, and stroke based on epidemiological data. SSc may affect the blood vessels that supply the heart resulting in myocardial infarction. As a consequence, SSc patients have a higher risk of myocardial infarction than the general population.
Risk minimisation measures	Routine risk minimisation measures: EU-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 the respective indications Additional risk minimisation measures: None

Important potential risks

Venous thromboembolism	
Evidence for linking the risk to the medicine	In the clinical trials, the frequency of patients with VTE was similar between both treatment groups. 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/SSc/PF-ILD. 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, SSc-ILD, and PF-ILD patients compared to controls. This is probably explained by the fact that IPF, SSc-ILD, and PF-ILD 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. Autoimmune diseases such as SSc have been associated with an increased risk of VTE.
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures: None
Arterial thromboembolism excluding myocardial infarction	
Evidence for linking the risk to the medicine	There was no evidence from the clinical trial programme with Ofev to suggest that ATE excluding myocardial infarction is an important identified risk in patients with IPF/SSc/PF-ILD. Nevertheless, the risk of ATE resulting from the drug class (TKIs with VGEF inhibition) cannot entirely be ruled out, and so ATE excluding MI is considered an important potential risk.
Risk factors and risk groups	Indication IPF: Based on the low number of patients affected, no clinically meaningful difference in frequency of arterial thromboembolism was observed in the analysed subgroups. There is an increased risk within the IPF population for cardiovascular disease, including coronary artery disease, myocardial infarction, and stroke based on epidemiological data. Indication SSc-ILD: SSc may affect the blood vessels that supply the heart resulting in myocardial infarction. As a consequence, SSc patients have a higher risk of coronary artery disease and myocardial infarction than the general population.

	Studies have reported an increased risk of ischaemic stroke among patients with SSc explained by the deleterious effects of this disease in the blood vessels. Indication PF-ILD: Subgroup analyses showed similar results between treatment groups. No clinically meaningful difference in frequency of arterial thromboembolism was observed in the analysed subgroups.
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD Additional risk minimisation measures: None
Perforation	
Evidence for linking the risk to the medicine	In the IPF (INPULSIS) studies and in the PF-ILD study (INBUILD), the frequency of patients with GI perforation was very low. In SSc (SCENSIS) studies, no gastrointestinal perforations were observed in patients treated with Ofev.
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 EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures None
Hepatic failure	
Evidence for linking the risk to the medicine	In the clinical trials, hepatic failure did not occur. Liver enzyme and bilirubin elevations including DILI are

	identified risks of 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	Indication IPF: Based on the low number of patients affected, no clinically meaningful difference in frequency of hepatic failure was observed in the analysed subgroups. Indication SSc-ILD: Overlap of SSc and autoimmune hepatitis has been observed in the SSc population. Indication IPF-ILD: Subgroup analyses suggest, that Asian and patients with a low body weight (≤65 kg) may be at higher risk of hepatic failure events. No clinically meaningful differences were observed in the remaining subgroups.
Risk minimisation measures	Routine risk minimisation measures EU-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 the respective indications Additional risk minimisation measures None
Effect on bone development and growth if used off-label in paediatric patients <18 years-of-age	
Evidence for linking the risk to the medicine	In non-clinical studies on nintedanib, changes in bone development and growth plates were observed. In the InPedILD study, the frequency of paediatric patients with pathological findings bone imaging was similar across treatment groups.
Risk factors and risk groups	Risk factors for growth impairment in children with fibrosing ILD include the underlying chronic disease and treatment with corticosteroids.
Risk minimisation measures	Routine risk minimisation measures EU-SmPC section 4.2 and 4.8 (text to prevent off-label paediatric use) PL section 2 Lack of commercial availability of the paediatric formulation (25 mg capsule) Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Trial 1199-0378 See Section II.C of this summary for an overview of the

	post-authorisation development plan
Effect on teeth development if used off-label in paediatric patients <18 years-of-age	
Evidence for linking the risk to the medicine	In non-clinical studies on nintedanib, changes in tooth structure and function were observed. In the InPedILD study, the frequency of paediatric patients with pathological findings on dental examination was similar across treatment groups.
Risk factors and risk groups	Patients at greater risk for the event of 'Stunted growth of dental root' include children aged 0 to 6 years and patients with underlying disorders which impact root development (such as dental trauma, Down syndrome, or Turner syndrome).
Risk minimisation measures	Routine risk minimisation measures EU-SmPC section 4.2 and 4.8 (text to prevent off-label paediatric use) PL section 2 Lack of commercial availability of the paediatric formulation (25 mg capsule) Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Trial/ 1199-0378 See Section II.C of this summary for an overview of the post-authorisation development plan

Missing information

Treatment of SSc-ILD patients with pulmonary hypertension	
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which 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

Trial 1199-0378
Purpose of the study: To collect additional safety data of nintedanib in children and adolescents with clinically significant fibrosing ILD for at least 2 years.

The main objective of the trial is to assess the safety and tolerability of long-term treatment with nintedanib in paediatric patients with clinically significant fibrosing ILD, as follows:

- Primary endpoint: incidence of treatment emergent adverse events over the whole trial

- Further safety endpoints: incidence of treatment-emergent pathological findings of epiphyseal growth plate on imaging over 24 weeks, over 52 weeks and over the whole trial; incidence of treatment-emergent pathological findings on dental examination or imaging over 24 weeks, over 52 weeks and over the whole trial.

ABBREVIATIONS

AE	Adverse event
ATE	Arterial thromboembolism
DILI	Drug-induced liver injury
DILIN	Drug-Induced Liver Injury Network
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
MI	Myocardial infarction
PF-ILD	Progressive fibrosing interstitial lung disease
PK	Pharmacokinetic
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis associated interstitial lung disease

TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor