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Summary of the risk management plan (RMP) for Ofev (nintedanib)

This is a summary of the risk management plan (RMP) for Ofev, which details the measures to be taken in order to ensure that Ofev is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Ofev, which can be found on Ofev's EPAR page.

Overview of disease epidemiology

Ofev is a medicine authorised for the treatment of adults with idiopathic pulmonary fibrosis (IPF). IPF is a long-term disease of the lungs characterised by the progressive deposition of collagen and fibrous tissue in the lungs. As a result, the lungs cannot work normally, which reduces the transfer of oxygen from the air into the blood. Patients with idiopathic pulmonary fibrosis have a persistent cough and shortness of breath that worsens over time.

In European countries, between 1 and 24 people out of every 100,000 had IPF between 1984 and 1998. The likelihood of having IPF increases with age, and men are more likely to develop IPF than women. People who smoke or have gastro-oesophageal reflux disease (a condition where stomach acid comes up from the stomach into the gullet) may be more likely to develop IPF. People who have often been exposed to dust (for example from metal, wood, stone, earth, and animals) may also be at an increased risk of IPF.

Summary of treatment benefits

The active substance in Ofev, nintedanib, blocks the activity of some enzymes known as tyrosine kinases that are involved in the processes that generate fibrous tissue in the lungs of patients with IPF.

Ofev has been compared with placebo (a dummy treatment) in two main studies involving a total of 1,066 patients with IPF. In both studies, the main measure of effectiveness was the decline in the functioning of the patients' lungs over the course of 1 year of treatment, measured by their forced vital capacity (FVC). FVC is the maximum amount of air the patient can breathe out forcefully after taking in a deep breath and this decreases as the condition gets worse.

In both studies, patients taking Ofev had a smaller decline in FVC than patients taking placebo, meaning that Ofev slowed down the worsening of the condition. The average FVC of patients before treatment was between 2600 and 2700 millilitre (ml). In the first study, the average decrease in FVC over 1 year was 115 ml in patients taking Ofev compared with a decrease of 240 ml in patients taking placebo. In the second study, the average decrease was 114 ml for Ofev compared with 207 ml for placebo. A further analysis of the results of the 2 main studies, which took into account that some patients stopped treatment, confirmed the benefits of Ofev over placebo, although the difference in FVC between the two was less pronounced.

Unknowns relating to treatment benefits

At present, there is little experience of using Ofev in pregnant or breastfeeding women; patients who have decreased liver function and severely reduced kidney function; patients who have wounds that are healing; patients of black ethnicity; and patients who are receiving a full dose of medicines to prevent blood clotting. However, there is no evidence to suggest that taking Ofev is not safe or effective in these patients. Also, there is limited experience on the combined use of Ofev and pirfenidone (another medicine for IPF marketed as Esbriet in the EU). The impact of taking Ofev on the safety and effectiveness of hormonal contraceptives is not known.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Diarrhoea	In the 2 main studies, more patients treated with Ofev had diarrhoea than patients receiving placebo (62% versus 18%). Most patients who had diarrhoea had mild or moderate diarrhoea.	Management of diarrhoea should start at its first signs. Patients should receive anti-diarrhoeal medicines, and also rehydration fluids (by mouth and/or into a vein, if necessary) to prevent or treat dehydration where appropriate. Patients with severe diarrhoea may require dose reduction and/or interruption of therapy with Ofev. Recommended dose reductions for Ofev are provided in the summary of product characteristics (SmPC).
Blood test results indicating possible decreased liver function (liver enzyme and bilirubin elevation)	In the 2 main studies, more patients treated with Ofev had blood test results indicating possible decreased liver function than patients receiving placebo (14% versus 3%). In most cases, these results were not a serious concern. In most patients, their blood test results returned to normal, without lasting liver damage.	Liver enzyme and bilirubin levels should be assessed before starting treatment and periodically monitored during Ofev therapy. If relevant increases are measured, dose reduction, treatment interruption, and/or the complete termination of Ofev treatment should be considered. Recommended dose reductions for Ofev are provided in the SmPC.

Important potential risks

Risk	What is known
Blood clots in the veins (venous thromboembolism)	Venous thromboembolism has been reported as an effect of medicines that block vascular endothelial growth factor receptors (VEGFR) when used for treating patients with cancer. Ofev also blocks VEGFR, and so the risk of venous thromboembolism cannot be ruled out. In the 2 main studies with Ofev, 1.2% of patients taking placebo and 1.1% of

Risk	What is known
	patients in the Ofev arm had venous thromboembolism.
Blood clots in the arteries (arterial thromboembolism)	In the 2 main studies with Ofev, 0.7% of patients taking placebo and 2.5% of patients taking Ofev had arterial thromboembolism. Although there were more patients with arterial thromboembolism in the Ofev group than in the placebo group, the relatively small number of events reported overall makes it difficult to say with certainty that taking Ofev increased the likelihood of having arterial thromboembolism.
Bleeding	Medicines that block VEGFR might be associated with an increased risk of bleeding, and so this risk cannot be ruled out for Ofev. In the 2 main studies with Ofev, more patients treated with Ofev than with placebo had bleeding events (10% versus 8%). However, since the difference is small, it is not possible to say with certainty whether taking Ofev increased the likelihood of a patient having bleeding events. Most patients who experienced bleeding had nose bleeds and/or bruises.
Perforation (hole) in certain internal organs of the digestive tract such as the stomach (gastrointestinal perforation)	Perforation of the digestive tract may be an effect of medicines that prevent or reduce the formation of new blood vessels (angiogenesis). As Ofev is also thought to reduce angiogenesis, the risk of perforation cannot be ruled out. In the 2 main studies with Ofev, 2 patients on Ofev had a perforation in the digestive tract. It is not possible to say with certainty whether taking Ofev increases the likelihood of a patient having a gastrointestinal perforation. Treatment with Ofev should be permanently stopped in patients who develop a perforation in the digestive tract.
Liver dysfunction (hepatic failure)	Events related to liver failure have been observed in studies with Ofev. In the main studies, 10 patients experienced events related to liver failure, fibrosis or cirrhosis (liver scarring), and other liver damage-related conditions compared with 1 patient taking placebo. Three of the 10 cases were considered serious and 5 patients were said to have recovered. Liver function tests should be performed before starting treatment with Ofev, and periodically thereafter. If any liver test elevations are associated with clinical signs or symptoms of liver injury, such as jaundice (yellowing of the skin and eyes), treatment with Ofev should be stopped.
Birth defects (teratogenicity)	Ofev has not been investigated in pregnant women. The properties of Ofev suggest that treatment may cause adverse effects on the embryo/fetus; this was confirmed in a non-clinical study. Therefore, women should not be treated with Ofev during pregnancy and should use adequate contraception during and for at least 3 months after the last dose of Ofev.
Heart (cardiac) failure	Some medicines belonging to the same class as Ofev may cause heart problems such as heart failure or congestive heart failure (heart disease where the heart cannot pump enough blood around the body). Very few patients in the Ofev clinical trial programme experienced heart failure, and there were no meaningful differences between patients treated with Ofev and those who received placebo.
Alteration of the	QT prolongation has been observed with some medicines belonging to the

Risk	What is known
electrical activity of the heart (QT prolongation)	same class as Ofev. However, there is no evidence that Ofev treatment increases the risk for QT prolongation based on clinical and non-clinical studies.

Missing information

Risk	What is known
Treatment of patients with decreased liver function (hepatic impairment)	Patients with decreased liver function (shown by aspartate aminotransferase and/or alanine aminotransferase and/or bilirubin more than 1.5 the upper limit of normal) were excluded from the clinical studies with Ofev. There is not enough information to fully assess whether there is a risk from Ofev treatment to patients with decreased liver function. Information from post-marketing experience will improve understanding of this issue.
Treatment of black patients	Specific races or ethnicities were not excluded from the clinical trials with Ofev in IPF. However, the proportion of black people in the 2 main studies with Ofev was low (2 patients, both in the Ofev treatment arm). There was no evidence to suggest that Ofev is less effective or less safe in black patients than in patients of other races or ethnicities. Nevertheless, more information from post-marketing experience is needed to confirm this.
Treatment of patients with healing wounds	Due to its mode of action, Ofev may slow the healing of wounds. In the 2 main studies with Ofev, wound healing was not identified as a safety concern. Nevertheless, further data is needed from post-marketing experience to fully exclude this potential safety issue.
Treatment of patients with severely reduced kidney function (severe renal impairment or end stage renal disease)	Only 1 patient in the 2 main studies with Ofev had severely reduced kidney function (severe renal impairment). There is not enough information to fully assess whether there is a risk from Ofev treatment to patients with severely reduced kidney function. Collecting more information from post-marketing experience will improve understanding of this issue.
Treatment of patients receiving a full dose of medicines to prevent blood clotting (full-dose therapeutic anticoagulation)	Due to its mode of action, Ofev may increase the risk of bleeding. As a precautionary measure, patients taking part in the 2 main studies with Ofev were not allowed to take any medications that prevented blood clotting. As a result, there is no information on the treatment of these patients with Ofev. Collecting more information from post-marketing experience will improve understanding of this issue.
Interaction of Ofev with hormonal contraceptives	The potential for interactions of Ofev with hormonal contraceptives has not been explored but is considered to be low. As a precaution, barrier methods (e.g. condoms) should be applied as a second form of contraception, to avoid pregnancy.
Taking Ofev at the same time as pirfenidone (concomitant	Information on taking Ofev and pirfenidone (another medicine used to treat IPF) at the same time is limited. In 13 Japanese patients taking both Ofev and pirfenidone, the uptake of pirfenidone by the body was not affected, but the uptake of Ofev tended to be reduced. However, no meaningful conclusions can

Risk	What is known
treatment)	be drawn as the study involved only a small number of patients who took both medications for only a short period of time.
Treatment of breastfeeding women	There is no information about whether breastfed babies could be exposed to Ofev through their mother's milk. Preclinical studies showed that small amounts of Ofev were secreted into milk of rats. Therefore, a risk cannot be excluded. Mothers should stop breastfeeding if they are taking Ofev.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Ofev can be found on Ofev's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Trial 1199.200 – nintedanib in volunteers with hepatic impairment.	To assess the pharmacokinetics (how nintedanib is handled by the body) and safety of nintedanib treatment in patients with hepatic (liver) impairment.	Missing information – treatment of patients with hepatic impairment.	Planned	May 2016 (first patient in planned for Nov 2014)
Trial 1199.229 – open-label nintedanib-pirfenidone drug-drug interaction study in patients with IPF	To evaluate pharmacokinetics of nintedanib and pirfenidone in patients with IPF	Missing information – simultaneous treatment (drug-drug interaction) with pirfenidone	Planned	Fourth quarter 2016

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 12-2014.