EU RISK MANAGEMENT PLAN FOR ESBRIET®/PIRFENIDONE

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Rationale for submitting an updated Risk Management Plan (RMP): This Esbriet E.U. RMP Version 12.1 is submitted in response to a request raised in the Assessment Report for procedure EMEA/H/C/002154/II/0074, which is the variation to extend the authorized indication from “treatment of adult patients with mild to moderate idiopathic pulmonary fibrosis (IPF)” to “treatment of adult patients with IPF.” The list of significant changes with the corresponding rationale is provided below.

Summary of significant changes in this RMP:

- Part II, Module SVII.3; Part II, Module SVIII; Part III, Module III.1: The following safety concerns have been removed:
  - Gastrointestinal symptoms
  - Risk of medication error in patients transferring between capsules and tablets
  - Patients with QT prolongation
  - Patients with underlying specific cardiac events

  None of these safety concerns are subject to additional pharmacovigilance activities and no additional risk minimisation measures are in place. The Summary of Product Characteristics (SmPC) describes the routine risk minimization measures in place for Gastrointestinal symptoms, and these symptoms are well-recognized and well-characterized. Following continued post-marketing monitoring by the Marketing Authorisation Holder (MAH), no new safety signal has emerged for the other safety concerns. Therefore, it is considered that at this stage of the product life cycle these safety concerns can be removed from the RMP. The MAH will continue to monitor such events via routine pharmacovigilance and present an evaluation of any newly emerging data via the appropriate regulatory channels.
- Part V: As per RMP template guidance, inclusion of references to the routine risk minimisation measures in the Patient Information Leaflet for the important identified risks (photosensitivity reaction and rash and drug-induced liver injury [DILI]) in Tables 15 and 17, respectively, and Part VI: Summary of the RMP.
  - Section 2 What you need to know before you take Esbriet – Warnings and Precautions
  - Section 3 How to take Esbriet – Dose reduction due to side effects
  - Section 4 Possible side effects
- Part II: Module SV: The methodology used to calculate post-authorization exposure and exposure data were updated in line with Periodic Benefit-Risk Evaluation Report (RDR 1113548); data lock point 27 February 2022.

Other RMP versions under evaluation:

None

Details of Currently Approved RMP: RMP Version number: 10.2

Approved with procedure: EMEA/H/C/002154/II/0066/G

Date of approval (opinion date): 01 October 2020

See Page 1 for e-signature and date.

Dr. Yusuf Tanrikulu (Deputy E.U. QPPV) Date

See Page 1 for e-signature and date.

PPD Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active substance(s) (INN or common name)	Pirfenidone
Pharmacotherapeutic group(s) (ATC Code)	L04AX05
Marketing authorization holder (or applicant)	Roche Registration Ltd.
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	Esbriet
Marketing authorization procedure	Centrally authorized procedure
Brief description of the product:	Chemical Class: Immunosuppressants, other immunosuppressants
	Summary of mode of action: The mechanism of action of pirfenidone has not been fully established. However, existing data suggest that pirfenidone exerts both antifibrotic and anti-inflammatory properties in a variety of in vitro systems and animal models of pulmonary fibrosis (bleomycin and transplant-induced fibrosis). Idiopathic pulmonary fibrosis is a chronic fibrotic and inflammatory pulmonary disease affected by the synthesis and release of pro-inflammatory cytokines including TNF-α and IL-1β and pirfenidone has been shown to reduce the accumulation of inflammatory cells in response to various stimuli. Pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as, TGF-β and PDGF.

Table 1 Product Overview (cont.)

	Important information about its composition: Esbriet is available in capsule presentation (267 mg pirfenidone) and film-coated tablets (267 mg pirfenidone; 534 mg pirfenidone and 801 mg pirfenidone). The list of excipients for these presentations is given below: **Capsule:** Capsule content: Microcrystalline cellulose, Croscarmellose sodium, Povidone, Magnesium stearate Capsule shell: Titanium dioxide (E171), Gelatin Printing Inks: Brown S-1-16530 or 03A2 inks containing: Shellac, Iron oxide black (E172), Iron oxide red (E172), Iron oxide yellow (E172), Propylene glycol and Ammonium hydroxide. **Film-coated Tablets:** Tablet core: Microcrystalline cellulose, Croscarmellose sodium Povidone K30, Colloidal anhydrous silica, Magnesium stearate Film coat: Polyvinyl alcohol, Titanium dioxide (E171), Macrogol 3350, Talc 267 mg tablet: Iron oxide yellow (E172) 534 mg tablet: Iron oxide yellow (E172), Iron oxide red (E172) 801 mg Tablet: Iron oxide red (E172), Iron oxide black (E172)
Hyperlink to the Product Information	E.U. PI
Indication(s) in the EEA	Current: Esbriet is indicated in adults for the treatment of mild to moderate IPF.
	Proposed: Esbriet is indicated in adults for the treatment of IPF.
Dosage in the EEA	Current: The recommended daily dose of Esbriet for patients with IPF is 801 mg TID with food, for a total of 2403 mg/day.
	Proposed: None
Pharmaceutical form(s) and strengths	Current: Film-coated tablets containing 267 mg, 534 mg, and 801 mg pirfenidone. Hard capsule containing 267 mg of pirfenidone
	Proposed: None
Is or will the product be subject to additional monitoring in the E.U.?	No

EEA = European Economic Area; EU = European Union; IL-1β = interleukin–1-beta; IPF = idiopathic pulmonary fibrosis; PDGF = platelet-derived growth factor, RMP = Risk Management Plan; TGF-β = transforming growth factor-beta; TID = 3 times a day; TNF-α = tumor necrosis factor-alpha.

ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
ALAT	Latin American Thoracic Association
ATS	American Thoracic Society
CrCl	creatinine clearance
DHPC	Dear Healthcare Professional
DIL	Dear Investigator Letter
DILI	drug-induced liver injury
DLco	carbon monoxide diffusing capacity
DLP	data lock point
DSR	Drug Safety Report
ERS	European Respiratory Society
E.U.	European Union
FVC	forced vital capacity
GAP	gender, age, physiology
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HRCT	high resolution computed tomography
IBD	international birth date
IPF	idiopathic pulmonary fibrosis
JRS	Japanese Respiratory Society
LFT	liver function test
MAH	Marketing Authorization Holder
NAC	N-acetylcysteine
NPP	Named Patient Program
NSAID	non-steroidal anti-inflammatory drug
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PYE	patient years of exposure
RMP	Risk Management Plan
RUCAM	Roussel Uclaf Causality Assessment Method
SMQ	Standardised MedDRA Query
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

Abbreviation	Definition
UIP	usual interstitial pneumonia
ULN	upper limit of normal
UV	ultraviolet
UVA/B	ultraviolet A/B

PART II: SAFETY SPECIFICATION

PART II: MODULE SI – EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Idiopathic Pulmonary Fibrosis

Incidence and Prevalence

The prevalence and incidence of idiopathic pulmonary fibrosis (IPF) varies across studies, depending on the case definition and the population studied. The annual incidence of IPF has been estimated as 6.8–17.4 per 100,000 in the United States and 0.22–7.4 per 100,000 in the European Union (E.U.). Prevalence estimates range from 14.0–63.0 per 100,000 in the United States and from 1.25–23.4 per 100,000 in the E.U. (Raghu et al. 2006; Fernández Pérez et al. 2010; Nalysnyk et al. 2012).
Idiopathic pulmonary fibrosis is most prevalent in middle-aged and elderly patients, and most studies have found a higher frequency in men than in women (Nalysnyk et al. 2012). Symptoms have usually been present for at least 6 months before the diagnosis was made.

A systematic review of 34 studies (Hutchinson et al. 2015) provides data from 21 countries. This review shows an increasing trend in worldwide incidence rates over time and also that rates are converging across countries. In studies since 2000, the estimated incidence rate of IPF ranges from 3–9 cases per 100,000 per year for Europe and North America, and is lower in East Asia and South America.

For Europe, results from large database studies in Denmark and the United Kingdom indicate that incidence rates of IPF range from 5.28–8.65 per 100,000 per year (age-adjusted estimates range from 2.91–4.17 per 100,000 per year). Hutchinson and Gribbin have reported an IPF incidence rate of 4.6 per 100,000 person-years in the United Kingdom and have suggested that more than 4000 new cases of IPF are diagnosed each year in the United Kingdom (Gribbin et al. 2006; Hutchinson et al. 2015). Results of regional studies across Europe provide lower rates.

While the criteria for the diagnosis of IPF have been updated (American Thoracic Society [ATS]/European Respiratory Society [ERS]/Japanese Respiratory Society [JRS]/Latin American Thoracic Association [ALAT] 2011; Raghu et al. 2018), they remain generally consistent with the 2000 ATS/ERS Consensus Statement (ATS/ERS 2000) and do not meaningfully affect prevalence estimates.
The Orphanet Report of May 2014 cites the prevalence of IPF in Europe as 11.5 cases in 100,000 persons.

Demographics

According to the ATS/ERS Consensus Classification of the Idiopathic Interstitial Pneumonias, IPF occurs in adults and predominately in patients > 50 years of age. Two-thirds of patients with IPF are over the age of 60 years at the time of presentation

and the mean age at diagnosis is 66 years. The incidence of the disease increases with older age (ATS/ERS 2000).

In general, the incidence of IPF is slightly higher in the male population than in females (Coultas et al. 1994; Thomeer et al. 2001; Gribbin et al. 2006). In a population-based study of adult patients with IPF in Olmsted County, Minnesota (1997–2005), the age and sex-adjusted incidence rate was 8.8 per 100,000 (narrow criteria) and 17.4 per 100,000 (broad criteria) person-years. The age-adjusted incidence rate was higher in men than in women, and among patients aged 70–79 years (Fernández Pérez et al. 2010).

The Main Existing Treatment Options

Pirfenidone and nintedanib are the only two approved treatment options for IPF. Pirfenidone was the first treatment that gained approval for IPF in the E.U. in 2011, with nintedanib, subsequently approved in 2014.

The 2011 ATS/ERS guidelines (which predated the E.U. approval of pirfenidone) recommend oxygen supplementation as required and pulmonary rehabilitation (ATS/ERS/JRS/ALAT 2011). According to the guideline pharmacological therapy, if elected, should be based on individualized discussions with patients. Although lung transplantation may be an additional therapeutic option, patients with IPF are often ineligible for transplantation.

An update to the ATS/ERS/JRS/ALAT guidelines, published in April 2015, acknowledges the significant advances made in the clinical management of IPF. New evidence for treatment recommendations was reviewed, and updated conditional treatment recommendations were provided in favor of the use of either pirfenidone or nintedanib. Strong recommendations were made against the use of other commonly prescribed therapies, including corticosteroid monotherapy, N-acetylcysteine (NAC) therapy, and combined corticosteroid (e.g., azathioprine or cyclophosphamide) therapy (Raghu et al. 2015). Many national IPF guidelines and position statements have been issued in 2017 based on the international guidelines. The published guidelines by German, Spanish, French, Nordic countries, Swiss and Australian expert groups also positively recommend the use of pirfenidone and nintedanib in the clinical management of IPF (Behr et al. 2017; Cottin et al. 2017; Funke-Chambour et al. 2017; Jo et al. 2017; Sköld et al. 2017; Xaubet et al. 2017). In 2018, the guideline updated the diagnostic criteria for IPF (Raghu et al. 2018). Previously defined patterns of usual interstitial pneumonia (UIP) were redefined to patterns of UIP, probable UIP, indeterminate for UIP, and alternate diagnosis.

Risk Factors for the Disease

A variety of genetic and environmental risk factors have been implicated as potential causes of IPF, including smoking and exposure to metal and wood dust, but no definitive

causes have been established as the initiating factor for the development of this disease (ATS/ERS 2000).

Natural History of the Indicated Condition in the (Untreated) Population

Disease Classification

Formal classification of IPF severity does not currently exist. In 2011, the first evidence-based clinical guidelines were established to help clinicians diagnose and manage IPF (Raghu et al. 2011). Despite updates to the therapeutic and diagnostic guidelines for IPF (Raghu et al. 2015; 2018), there continues to be no formal guidance on disease staging. Likely, a major factor in the lack of definitive staging criteria is the fact that IPF progression is not always linear and patients may have long periods of stable disease followed by rapid decline.

Despite this, it is generally accepted that forced vital capacity (FVC) and decrease in carbon monoxide diffusing capacity (DLco) are significant predictors of mortality in IPF. In contrast, high resolution computed tomography (HRCT) pattern of UIP (probable vs. definite) is not (Yamauchi et al. 2016; Raghu et al. 2017; Hyldgaard et al. 2020). One proposed staging method, GAP (gender, age, physiology) staging (Ley et al. 2012), incorporates the use of FVC and DLco, in addition to gender and age, into its prediction of mortality risk. Gender, age, physiology Stage 1 reflects the lowest risk of 1 and 3-year mortality, whereas Stage III is the highest risk. However, the GAP staging fails to predict functional changes over the next year (Ley et al. 2016).

The official classification of disease severity in Japan uses the J system, has been discussed recently, and has been evaluated against a revised J system as well as the GAP system (Kondoh et al. 2017). The revised J system and GAP system have been found to be valuable tools to predict mortality and manage IPF. However, the J system has not been used in any pivotal trials for IPF elsewhere and is only used in clinical practice in Japan.

While there is no standardized definition for mild, moderate and severe disease, clinical studies have used an FVC threshold of 50%–55% predicted and a DLco threshold of 35%–40% predicted to separate mild-to-moderate patients from those with severe disease (King et al. 2011; Noble et al. 2011; Richeldi et al. 2011; Raghu et al. 2012). Due to its relentlessly progressive nature and poor prognosis, the term “mild-to-moderate” IPF potentially misrepresents the seriousness of IPF, as it only refers to the functional status of a patient at the moment of evaluation (e.g., FVC or DLco values), but any patient with even very limited functional impairment (“mild” IPF) at diagnosis will progress to worse functional impairment and ultimately respiratory failure and death.

Mortality and Morbidity

The classic clinical phenotype of IPF is one of slowly progressive decline in lung function and worsening dyspnea, leading to death within 2–5 years of diagnosis (Bjoraker et al. 1998; Ley et al. 2011; Navaratnam et al. 2011; Strand et al. 2014). Historical estimates suggest that 38%–55% of patients with IPF die of IPF-related causes (Turner-Warwick et al. 1980; Johnston et al. 1990). However, in a Phase III trial of interferon gamma-1b (IFNγ-1b) (Actimmune), 89% of deaths in placebo patients were considered by the study's principal investigators to be related to IPF (Martinez et al. 2005).

In IPF, hospital admissions are often due to respiratory worsening and are associated with reduced survival. At least half of hospitalizations are thought to be due to acute exacerbations of IPF, defined as respiratory worsening over less than 1 month without an identifiable secondary cause, such as infection. Based mostly on retrospective studies, the annual incidence rate of acute exacerbations of IPF ranges from approximately 5%–20%, with a mortality rate of 20%–100% (Ley and Collard 2013).

Outcome of the (Untreated) Target Disease

Idiopathic pulmonary fibrosis is a rapidly progressive disease with an extremely poor prognosis. Median survival following diagnosis has been reported to be as low as 2–5 years (Cottin 2012). The clinical course is challenging to predict. For some patients the course of disease is rapid, with fatal respiratory failure evolving over a few months (Selman et al. 2007). Other patients have a gradual progression over years, followed by acute exacerbations associated with abrupt and often fatal hypoxemic respiratory failure (Collard et al. 2007). Spontaneous remissions do not occur with IPF, and 10-year survival is less than 15% (Lynch and Belperio 2012). Clinically, IPF usually presents insidiously, with the gradual onset of a non-productive cough and dyspnea. Dyspnea is usually the most prominent and disabling symptom and is progressive in nature (ATS/ERS 2000).

Pregnancy and Breastfeeding

Idiopathic pulmonary fibrosis is a disease of the elderly, and two-thirds of patients with IPF are older than 60 years at the time of presentation (ATS/ERS 2000).

Therefore, pregnancy is a rare occurrence in the IPF population and no reliable data are available concerning the use of pirfenidone in pregnant women (see Section SII).

Important Co-Morbidities

The most common IPF comorbidities are coronary artery disease, gastroesophageal reflux disease (GERD), obstructive sleep apnea, lung cancer and pulmonary infection.

Steroid-related complications resulting from concomitant use with pirfenidone, include hypertension, peptic ulcer, osteoporosis, tuberculosis, and diabetes (Turner-Warwick et al. 1980). Complications of other pharmacological therapies used in the treatment of IPF (off-label agents such as azathioprine and cyclophosphamide) include bone marrow depression, increased susceptibility to infections, increased risk for malignancies, gastrointestinal (GI) distress (e.g., nausea, vomiting, anorexia, and/or diarrhea), and liver toxicity (with azathioprine) (Winterbauer et al. 1978; Raghu et al. 1991; Zisman et al. 2000).

Gastroesophageal reflux disease is a potential risk factor for IPF. Present IPF treatment guidelines give a conditional recommendation for anti-acid therapies (AAT) with very low confidence in estimates of effect (Raghu et al. 2015).

Present IPF guidelines suggest that clinicians should not use NAC monotherapy in patients with IPF (conditional recommendation, low confidence in estimates of effect).

After pooling the results of 3 randomized, controlled trials, no significant benefit on mortality was seen using NAC monotherapy for patients with IPF. There were no significant differences in FVC change, quality of life or adverse outcomes (Raghu et al. 2015).

PART II: MODULE SII – NONCLINICAL PART OF THE SAFETY SPECIFICATION

TOXICITY

Repeat-Dose Toxicity

Gastrointestinal System

In repeat-dose toxicity studies in dogs, vomiting was commonly seen at high doses of pirfenidone.

Central Nervous System

In repeat-dose oral studies in rats (gavage) and dogs, the principal clinical findings were transient CNS-related clinical effects.

Platelet Effects

Increased platelet levels were seen in some repeat-dose toxicity studies in the mouse, rat and dog.

Hepatic System

Increased alkaline phosphatase (up to 3-fold higher than control values), hepatic enzyme induction (determined in 2 studies), increased liver weight (up to 4-fold higher than control values) and hepatocellular hypertrophy were observed in repeat-dose dog toxicity studies conducted with pirfenidone.

Relevance to Human Usage

No, for platelet effects and hepatic system.

Yes, for GI system and CNS.

Discussion

Gastrointestinal effects are a recognized adverse reaction associated with clinical use of pirfenidone and are adequately addressed by clinical monitoring.

Central nervous system adverse reactions such as dizziness, fatigue, anorexia, and decreased appetite are recognized after pirfenidone administration. Anorexia and decreased appetite might contribute to weight loss, which is an identified risk of pirfenidone administration. It is considered that potential CNS effects of pirfenidone are adequately addressed by clinical monitoring.

The nonclinical hepatic findings (increased alkaline phosphatase, increased liver weight and hepatocellular hypertrophy) in repeat-dose dog studies are considered to be an adaptive response to hepatic metabolism of pirfenidone and induction of CYP enzymes. These findings are not considered relevant for human usage.

The increases in platelet count in these studies were considered slight in magnitude, were not seen in all studies, and were not considered to be toxicologically meaningful. Review of safety data from marketing authorization holder (MAH)-sponsored Phase III studies revealed no clinically-significant effects on platelets. While a review of data from Shionogi reveals that there were few incidents of decreased platelet counts in their post-marketing surveillance program, analysis of the MAH post-marketing data for patients exposed to pirfenidone indicated that increases in platelet counts were not evident after over 63,000 world-wide patient years of exposure (PYE). This potential risk was removed from the E.U. RMP in 2016.

Reproductive/Developmental Toxicity

Dietary Fertility Study

In the dietary fertility study in rats, body weight and food consumption were decreased in both sexes; in females, these correlated with depressed gravid uterine weights, and fetuses with reduced body weights and fetal immaturity (soft tissue and skeletal variations). Similar changes were not observed in the fertility study in rats with gavage administration, which used similar dose levels.

At high doses (≥450 mg/kg/day), rats exhibited a prolongation of estrous cycle and a high incidence of irregular cycles.

Pre- and Post-Natal Study

In the pre- and post-natal study conducted in rats, a prolongation of gestation and reduction in fetal viability were observed at the high dose of 1000 mg/kg/day. Except for reduced body weights during the nursing period at doses > 300 mg/kg/day, there were no adverse effects on the postnatal development of offspring.

Relevance to Human Usage

Not known.

Discussion

The reduced fetal weights were attributed to maternal toxicity (in the absence of effects on the number of implantations and pre- and post-implantation losses) rather than any direct effect on the fetus. The observed fetal variations were considered to result from secondary maternal effects (nutritional stress) which resulted in slightly delayed fetal development. The relevance of the findings in the dietary study in rats to humans is not known at this time.

The relevance of findings (from high dose study) in rats to the menstrual cycle in humans is not known at this time. This finding is included in Section 5.3 (Preclinical Safety Data) of the Summary of Product Characteristics (SmPC).

The prolongation of the gestation period at the high dose (1000 mg/kg/day) in rats suggests that difficulties in parturition may have been experienced by the dams, resulting in adverse effects on pups with consequent loss of live pups. The relevance of these findings in rats to humans is not known at this time. These are included in Sections 4.6 (Fertility, Pregnancy, and Lactation) and 5.3 (Preclinical Safety Data) of the SmPC.

Photogenotoxicity

Pirfenidone was not photomutagenic in the Ames bacterial reverse mutation assay but was photoclastogenic when exposed to ultra violet (UV) A (UVA) in the Chinese hamster lung cell assay.

Relevance to Human Usage

Yes

Discussion

Skin reactions and rash have been identified in clinical trials as risks for pirfenidone. No increase in skin cancer was observed in patients treated with pirfenidone as compared with placebo in the Phase III studies. Additionally, there has been no indication of a safety signal related to skin cancer in either of the safety studies

(PIPF-002 and PIPF-012) or in the post-marketing experience with pirfenidone in Japan. The incidence of cancerous and precancerous skin lesions remains low during extended periods of treatment with pirfenidone. There is no evidence of a relationship between preexisting neoplastic or precancerous skin lesions and the subsequent occurrence of skin-related treatment-emergent adverse events (TEAEs) due to treatment with pirfenidone.

Neoplastic sequelae are not considered to present a potential risk to patients. The potential photogenotoxicity effects of pirfenidone are; therefore, adequately addressed by clinical monitoring. The positive photoclastogenic finding has been included in Section 5.3 (Preclinical Safety Data) of the SmPC.

Phototoxicity

There was no evidence of photosensitivity with pirfenidone but transient phototoxic effects were noted in the skin of guinea pigs after oral administration of pirfenidone concomitant to exposure to UVA/UV B (UVB). These skin effects were mitigated with topical application of sunscreen agents. In hairless mice treated orally with pirfenidone and exposed to UV, reversible mild acanthosis and mild single cell necrosis were observed in the epidermis of the auricle and the dorsal skin. There was no systemic toxicity.

Relevance to Human Usage

Yes

Discussion

Photosensitivity reactions are an identified risk with pirfenidone use in humans (see Section SVII.3.1). This risk can be minimized by educating patients on how to avoid exposure to sunlight and all other sources of UV light and use appropriate sun blocks. Dose modification may also help to mitigate the risk. Patients with mild or moderate symptoms in whom the dose has been modified can be rechallenged with full dose pirfenidone. Therefore, it is considered that potential phototoxicity effects of pirfenidone are adequately addressed by clinical monitoring.

Carcinogenicity

Carcinogenicity studies in mice and rats revealed an increase in the incidence of liver cell tumors in both species and an increase in uterine tumors in rats. These increased tumors are attributed to rodent and rat specific mode of actions, respectively.

Relevance to Human Usage

Not known

Discussion

The uterine tumors observed in rats are a well-documented, species-specific finding due to prolactin level reduction and a shift in the estrogen/progesterone ratio, with no correlation in humans. Similarly, hepatocellular tumors observed in rodent studies of pirfenidone were described as secondary to phenobarbital-type induction of drug metabolizing, CYP450 enzymes in the liver. Although evaluation of epidemiologic studies of several marketed drug products with these animal findings suggests no indication of an increased risk in development of either tumor type in humans, the relevance of these rodent tumors to humans is not known at this time.

GENERAL SAFETY PHARMACOLOGY

Gastrointestinal System

In nonclinical safety pharmacology studies, decreased gastric emptying and decreased small intestinal transport were observed in rats after oral administration of pirfenidone.

Relevance to Human Usage

Yes

Discussion

Gastrointestinal effects (diarrhea, dyspepsia, nausea, vomiting, GERD, and abdominal discomfort) are a recognized adverse reaction associated with clinical use of pirfenidone. These symptoms can be reduced by taking pirfenidone with food. If symptoms persist, a dose reduction regime can be applied. Therefore, it is considered that potential GI effects of pirfenidone in humans are adequately addressed by clinical monitoring.

Cardiovascular System

In two cardiovascular safety studies in rats, intraduodenal administration of pirfenidone at high doses (300 mg/kg) did evoke occasional arrhythmias; however, these were episodic in nature and were not observed in any dog study.

Relevance to Human Usage

No

Discussion

The clinical relevance of the findings in rats is uncertain with respect to both the route of administration utilized and the fact that the mechanisms of cardiac repolarization are different in rats compared to dogs and humans. The arrhythmias observed in rat safety pharmacology studies are considered to have no relevance to human usage. Review of safety data from the Phase III studies, including central review of ECGs, along with post-marketing safety data from Japan, post-marketing safety data covering over

63,000 PYE of world-wide exposure, and a long-term prospective study following patients exposed to pirfenidone under real-world conditions have shown no clear sign of cardiac toxicity.

Central Nervous System

Pirfenidone has been shown to interact with the dopamine transporter with in vitro IC_{50}/Ki values of 988/785 μM pirfenidone (183/145 μg/mL). The clinical steady state maximum observed concentration (C_{max}) is 14.7 μg/mL after a single oral dose of 2403 mg/day. In safety pharmacology studies, transient neurobehavioral effects, including sedation, abnormal posture, abnormal limb position, staggering gait, ptosis, and hypothermia were seen in mice administered single oral doses of pirfenidone. At a 300 mg/kg oral dose, pirfenidone caused a prolongation of pentobarbital-induced sleep time.

Relevance to Human Usage

Yes

Discussion

Central nervous system adverse reactions such as dizziness, fatigue, anorexia, and decreased appetite are recognized after pirfenidone administration. Anorexia and decreased appetite might contribute to weight loss, which is an identified risk of pirfenidone administration. To minimize the risk of dizziness, patients are advised to take pirfenidone with food. Patients are instructed to learn how they react to pirfenidone before they drive a vehicle or operate machinery. To minimize the risk of weight loss associated with anorexia and decreased appetite, health care professionals and patients will be advised to monitor the patient's weight and to use dietary supplementation where necessary. Therefore, it is considered that potential CNS effects of pirfenidone are adequately addressed by clinical monitoring.

Pregnancy and Lactation

In lactating animals, excretion of pirfenidone and/ or its metabolites in milk occurs with the potential for the accumulation of pirfenidone and/or its metabolites in milk.

In pregnant animals, placental transfer of pirfenidone and/or its metabolites occurs with the potential for the accumulation of pirfenidone and/or its metabolites in amniotic fluid.

Relevance to Human Usage

Not known

Discussion

The relevance of these findings in rats to humans is not known at this time.
These findings are included in the SmPc in Section 4.6 (Fertility, Pregnancy, and

Lactation) and Section 5.3 (Preclinical Safety Data). The outcome of all reported human pregnancies, where mother and fetus are exposed to pirfenidone, are sought as part of the routine obligations of the MAH. There have been no reports of adverse pregnancy or lactation outcomes in the context of pirfenidone exposure in the safety database to date.

PART II: MODULE SIII –CLINICAL TRIAL EXPOSURE

Clinical trial exposure (prior to marketing authorization) data are presented below by overall duration on treatment in Table 2, overall mean daily dose in Table 3, by total duration and mean daily dose in Table 4, by sex in Table 5, by age in Table 6 and by race in Table 7. Clinical trial exposure data in special population are also presented in Table 8 and Table 9.

The Pirfenidone Patient Subset contains pooled data from 1299 unique patients. This includes patients treated with at least 1 dose of pirfenidone in the 3 randomized, double-blind, placebo-controlled studies (Phase III Studies PIPF-004, PIPF-006 and PIPF-016, N =623 patients (2403 mg/day); and 87 patients from Study PIPF-004 (1197 mg pirfenidone) for an overall N =710), as well as the uncontrolled Phase II study (PIPF-002, N =83) and the uncontrolled Phase III extension study (PIPF-012, N =506). In this subset patients entering the open-label extension following participation in these placebo-controlled studies were counted only once.

Exposure-adjusted analyses of pooled clinical trials in IPF confirmed that the safety and tolerability profile of pirfenidone in patients with IPF with advanced disease (N =366) is consistent with that established in patients with IPF with non-advanced disease (N =942) (Pirfenidone Summary of Clinical Safety [SCS] 2021).

Data tables for exposure in special population has been presented for patients with renal impairment (Study PIPF-009) and patients with hepatic impairment (Study PIPF-011).

Table 2 Overall Duration on Treatment in Pirfenidone Patient Subset: Studies PIPF-002, PIPF-004, PIPF-006, PIPF-012, and PIPF-016

	Pirfenidone Patients (n=1299)
Duration on Study Treatment (Weeks)	
n	1299
Mean	126.9
25th Percentile	37.7
Median	86.0
75th Percentile	209.0
SD	110.91

Table 2 Overall Duration on Treatment in Pirfenidone Patient Subset: Studies PIPF-002, PIPF-004, PIPF-006, PIPF-012, and PIPF-016 (cont.)

	Pirfenidone Patients (n =1299)
Min, Max	>0, 519
Total Patient (mean × n) Weeks	164881
Total PYY	3160
Number of Patients on Study Treatment, n (%)	
>0 to <2 Weeks	18 (1.4%)
2 to <6 Weeks	40 (3.1%)
6 to <18 Weeks	109 (8.4%)
18 to <30 Weeks	107 (8.2%)
30 to <42 Weeks	74 (5.7%)
42 to <54 Weeks	76 (5.9%)
54 to <66 Weeks	99 (7.6%)
66 to <78 Weeks	76 (5.9%)
78 to <114 Weeks	185 (14.2%)
≥114 Weeks	515 (39.6%)

Max=maximum; Min =minimum; n = number of patients; PYE=patient years of exposure.

Table 3 Overall Mean Daily Dose in Pirfenidone Patient Subset: Studies PIPF-002, PIPF-004, PIPF-006, PIPF-012, and PIPF-016

	Pirfenidone Patients (n=1299)
Mean Daily Dose (mg)	
n	1278 [a]
Mean (SD)	2053.8 (484.90)
Median	2270.4
Q1, Q3	1879.3, 2368.1
Min, Max	25, 3600
Missing [a]	21
Number of Patients with a Mean Daily Dose, n (%)	
>0 to ≤ 1000 mg/Day	62 (4.8%)
>1000 to ≤ 1400 mg/Day	94 (7.2%)
>1400 to ≤ 1800 mg/Day	139 (10.7%)
>1800 to ≤ 2200 mg/Day	228 (17.6%)
>2200 to ≤ 2600 mg/Day	736 (56.7%)
>2600 mg/Day	19 (1.5%)
Missing [a]	21

Max = maximum; Min = minimum; n = number of patients; Q1, Q3 = 25th and 75th percentile, respectively.

[a] Data not available for 4 patients.

Table 4 Exposure to Pirfenidone According to Total Duration and Mean Daily Dose in Pirfenidone Patient Subset: Studies PIPF-002, PIPF-004, PIPF-006, PIPF-012, and PIPF-016

	Number of Patients, n (%)					
	Mean Daily Dose (mg)					
Total Duration (weeks)	**>0 to ≤1000**	**>1000 to ≤1400**	**>1400 to ≤1800**	**>1800 to ≤2200**	**>2200 to ≤2600**	**>2600**
Pirfenidone Patients (n=1278) [a]						
>0 to <2	0	0	0	0	0	0
2 to <6	1 (0.1%)	2 (0.2%)	4 (0.3%)	5 (0.4%)	25 (2.0%)	0
6 to <18	8 (0.6%)	14 (1.1%)	15 (1.2%)	12 (0.9%)	59 (4.6%)	1 (0.1%)
18 to <30	10 (0.8%)	13 (1.0%)	16 (1.3%)	20 (1.6%)	47 (3.7%)	1 (0.1%)
30 to <42	2 (0.2%)	8 (0.6%)	10 (0.8%)	15 (1.2%)	38 (3.0%)	1 (0.1%)
42 to <54	4 (0.3%)	4 (0.3%)	9 (0.7%)	14 (1.1%)	43 (3.4%)	2 (0.2%)
54 to <66	4 (0.3%)	7 (0.5%)	7 (0.5%)	20 (1.6%)	60 (4.7%)	1 (0.1%)
66 to <78	3 (0.2%)	4 (0.3%)	6 (0.5%)	12 (0.9%)	50 (3.9%)	1 (0.1%)
78 to <114	10 (0.8%)	15 (1.2%)	14 (1.1%)	27 (2.1%)	116 (9.1%)	3 (0.2%)
≥114	20 (1.6%)	27 (2.1%)	58 (4.5%)	103 (8.1%)	298 (23.3%)	9 (0.7%)
Total (Any Duration)	**62 (4.9%)**	**94 (7.4%)**	**139 (10.9%)**	**228 (17.8%)**	**736 (57.6%)**	**19 (1.5%)**

n = number of patients.

[a] Dose data not available for 21 patients.

Table 5 Overall Duration on Pirfenidone Treatment by Sex in Pirfenidone Patient Subset: Studies PIPF-002, PIPF-004, PIPF-006, PIPF-012, and PIPF-016

	Males (n=968)	Females (n=331)
Number of Patients on Study Treatment, n (%)		
>0 to <2 Weeks	11 (1.1%)	7 (2.1%)
2 to <6 Weeks	32 (3.3%)	8 (2.4%)
6 to <18 Weeks	76 (7.9%)	33 (10.0%)
18 to <30 Weeks	87 (9.0%)	20 (6.0%)
30 to <42 Weeks	59 (6.1%)	15 (4.5%)
42 to <54 Weeks	51 (5.3%)	25 (7.6%)
54 to <66 Weeks	75 (7.7%)	24 (7.3%)
66 to <78 Weeks	64 (6.6%)	12 (3.6%)
78 to <114 Weeks	144 (14.9%)	41 (12.4%)
≥114 Weeks	369 (38.1%)	146 (44.1%)

n=number of patients.

Table 6 Overall Duration on Pirfenidone Treatment by Age in Pirfenidone Patient Subset: Studies PIPF-002, PIPF-004, PIPF-006, PIPF-012, and PIPF-016

	<65 years (n=421)	≥65 years (n=878)	≥75 years (n=285)
Number of Patients on Study Treatment, n (%)			
>0 to <2 Weeks	8 (1.9%)	10 (1.1%)	3 (1.1%)
2 to <6 Weeks	9 (2.1%)	31 (3.5%)	11 (3.9%)
6 to <18 Weeks	28 (6.7%)	81 (9.2%)	28 (9.8%)
18 to <30 Weeks	32 (7.6%)	75 (8.5%)	29 (10.2%)
30 to <42 Weeks	26 (6.2%)	48 (5.5%)	18 (6.3%)
42 to <54 Weeks	19 (4.5%)	57 (6.5%)	20 (7.0%)
54 to <66 Weeks	27 (6.4%)	72 (8.2%)	19 (6.7%)
66 to <78 Weeks	19 (4.5%)	57 (6.5%)	10 (3.5%)
78 to <114 Weeks	53 (12.6%)	132 (15.0%)	43 (15.1%)
≥114 Weeks	200 (47.5%)	315 (35.9%)	104 (36.5%)

n=number of patients.

Table 7 Overall Duration on Pirfenidone Treatment by Race in Pirfenidone Patient Subset: Studies PIPF-002, PIPF-004, PIPF-006, PIPF-012, and PIPF-016

	White (n=1127)	Non-White (n=172)
Number of Patients on Study Treatment, n (%)		
>0 to <2 Weeks	10 (0.9%)	8 (4.7%)
2 to <6 Weeks	31 (2.8%)	9 (5.2%)
6 to <18 Weeks	85 (7.5%)	24 (14.0%)
18 to <30 Weeks	86 (7.6%)	21 (12.2%)
30 to <42 Weeks	61 (5.4%)	13 (7.6%)
42 to <54 Weeks	65 (5.8%)	11 (6.4%)
54 to <66 Weeks	80 (7.1%)	19 (11.0%)
66 to <78 Weeks	60 (5.3%)	16 (9.3%)
78 to <114 Weeks	171 (15.2%)	14 (8.1%)
≥114 Weeks	478 (42.4%)	37 (21.5%)

n=number of patients.

A Phase I study (PIPF-009) was carried out, which was a single-dose, open-label, parallel-group study designed to compare the pharmacokinetics and safety of pirfenidone in subjects with mild to severe renal impairment compared with normal, healthy adults. Each subject received a single 801 mg dose of pirfenidone. The total numbers (with renal impairment) treated with pirfenidone, based on their screening creatinine clearance (CrCl) in mL/min were:

- Mild renal impairment (CrCl >50 and ≤80): 6 subjects, 4 male and 2 female, aged 59–79, mean 70.2 (SD 8.52) years
- Moderate renal impairment (CrCl ≥30 and ≤50): 7 subjects, 4 male and 3 female, aged 54–79, mean 67.7 (SD 8.26) years
- Severe renal impairment (CrCl <30): 7 subjects, 5 male and 2 female, aged 57–69, mean 64.9 (SD 4.60) years

Table 8 Overall Exposure of Pirfenidone Treatment in Special Population (Renal Impairment) – Study PIPF–009

Variable	Mild (n =6)	Moderate (n =7)	Severe (n =7)	Total (n =20)
Dose	**Single Dose (801 mg)**	**Single Dose (801 mg)**	**Single Dose (801 mg)**	**Single Dose (801 mg)**
Age at Time of Dosing (years)				
n	6	7	7	20
Mean	70.2	67.7	64.9	67.5
SD	8.52	8.26	4.60	7.22
Median	70.5	68.0	67.0	67.5
Min, Max	59, 79	54, 79	57, 69	54, 79
Sex				
Male	4 (66.7%)	4 (57.1%)	5 (71.4%)	13 (65.0%)
Female	2 (33.3%)	3 (42.9%)	2 (28.6%)	7 (35.0%)
Primary Race				
Asian	1 (16.7%)	1 (14.3%)	0	2 (10.0%)
Black or African American	0	1 (14.3%)	3 (42.9%)	4 (20%)
Native Hawaiian or other Pacific Islander	0	0	1 (14.3%)	1 (5.0%)
White	5 (83.3%)	5 (71.4%)	3 (42.9%)	13 (65.0%)
Ethnicity				
Hispanic or Latino	3 (50.0%)	2 (28.6%)	4 (57.1%)	9 (45.0%)
Not Hispanic or Latino	3 (50.0%)	5 (71.4%)	3 (42.9%)	11 (55.0%)

Max = maximum; Min = minimum; n = number of patients.

Another Phase I study (PIPF-011) was carried out which was a single-dose, open-label, parallel-group study designed to compare the pharmacokinetics and safety of pirfenidone in subjects with moderate hepatic impairment, compared to normal, healthy adults. The study included 12 subjects with Child Pugh Class B (moderate) hepatic impairment (7 males and 5 females, aged 49–75, mean 58.7 [SD 7.4] years). Each subject received a single 801 mg dose of pirfenidone. Based on the results from this study, subjects with moderate hepatic impairment have, on average, exposure to pirfenidone 60% higher than normal subjects.

Table 9 Overall Exposure of Pirfenidone Treatment in Special Population (Hepatic Impairment) – Study PIPF–011

Variable	Moderate Hepatic Impairment (n = 12)
Dose	**Single Dose (801 mg)**
Age at Time of Dosing (years)	
n	12
Mean	58.7
SD	7.38
Median	57.5
Min, Max	49, 75
Sex	
Male	7 (58.3%)
Female	5 (41.7%)
Primary Race	
White	12 (100%)
Ethnicity	
Hispanic or Latino	5 (41.7%)
Not Hispanic or Latino	7 (58.3%)

Max = maximum; Min = minimum; n = number of patients.

PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 10 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
History of advanced cirrhosis or clinically significant liver disease.	Pirfenidone has not been studied in individuals with severe hepatic impairment and pirfenidone should not be used in patients with severe hepatic impairment.	No	Severe hepatic impairment or end stage liver disease is contraindicated in E.U. SmPC.
Known hypersensitivity to pirfenidone or to any of the components of study treatment.	Patients with hypersensitivity to the active substance or to any of the excipients should not receive treatment with pirfenidone.	No	Hypersensitivity to the active substance or to any of the excipients is a contraindication in the E.U. SmPC.
• PIPF-004 and 006: FEV1/FVC ratio < 0.7 after administration of bronchodilator. • PIPF-016: FEV1/FVC ratio < 0.8 after administration of bronchodilator.	To eliminate patients with other obstructive causes of pulmonary disease.	No	Pirfenidone is indicated for the treatment of IPF only.
Bronchodilator Response defined by an absolute increase of $\geq 12\%$ and an increase of 200 mL in the predicted FEV1 or FVC or both after bronchodilator use compared with the values seen before randomization.	To eliminate patients with other obstructive causes of pulmonary disease.	No	Pirfenidone is indicated for the treatment of IPF only.
Residual volume (RV) $> 120\%$ of predicted (before administration of bronchodilator).	To eliminate patients with other obstructive causes of pulmonary disease.	No	Pirfenidone is indicated for the treatment of IPF only.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
History of clinically significant environmental exposure known to cause pulmonary fibrosis (including but not limited to drugs, asbestos, beryllium, radiation, domestic birds).	To eliminate patients with known causes of pulmonary fibrosis.	No	Patients with this etiology of pulmonary fibrosis should not receive pirfenidone because it is indicated for patients with IPF.
Known explanation for interstitial lung disease, including but not limited to radiation, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, HIV, viral hepatitis and cancer.	To eliminate patients with known causes of pulmonary fibrosis.	No	Patients with this etiology of pulmonary fibrosis should not receive pirfenidone because it is indicated for patients with IPF.
Diagnosis of any connective tissue disease, including but not limited to scleroderma, systemic lupus erythematosus, and rheumatoid arthritis.	To eliminate patients with known causes of pulmonary fibrosis.	No	Patients with pulmonary fibrosis caused by connective tissue diseases should not receive pirfenidone because it is indicated for patients with IPF.
Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis.	To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	Standard clinical trial exclusion criterion for safety reasons.
The patient is expected to need and be eligible for a lung transplant within 72 weeks after randomization.	• To minimize the risk of premature withdrawal from the study. • To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	Specific requirement for the clinical trials.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Unable to undergo pulmonary function testing (according to the criteria set out in the protocol).	Would not be able to undergo the testing required as part of the clinical trial for efficacy assessment.	No	Specific requirement for the clinical trials.
Any history of malignancy likely to result in death or significant disability or likely to require significant medical or surgical intervention within the next 2 years (not including minor surgical procedures for localized carcinoma [e.g., basal cell carcinoma]).	To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	Standard clinical trial exclusion criterion for safety reasons.
Any condition other than IPF, which, in the opinion of the investigator, is likely to result in the death of the patient within the next 2 years.	To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	Standard clinical trial exclusion criterion for safety reasons.
History of unstable or deteriorating cardiac or pulmonary disease other than IPF within the previous 6 months, including but not limited to the following: • Myocardial infarction, unstable angina pectoris, coronary artery bypass surgery, or coronary angioplasty • Congestive heart failure requiring hospitalization	To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	Standard clinical trial exclusion criterion for safety reasons.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
• Uncontrolled arrhythmias • Asthma or chronic bronchitis requiring hospitalization in the last 6 months			
Any condition which might be significantly exacerbated by the known side effects associated with the administration of pirfenidone.	To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	Standard clinical trial exclusion criterion for safety reasons.
Poorly controlled diabetes (defined by glycosylated haemoglobin [HbA1C] > 10).	• To eliminate patients with risk factors for hepatic dysfunction. • To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	This criterion was not related to the safety of the patient population.
Pregnancy or lactation: Women of childbearing capacity were required to have a negative serum pregnancy test before treatment and must have agreed to maintain highly effective methods of contraception by practicing abstinence or by using at least 2 methods of birth control from the date of consent through the end of the study.	Standard clinical trial exclusion criteria for safety reasons.	No	It is highly unlikely that pregnant and lactating women receive this treatment (according to the label), therefore it is not relevant in clinical practice. This information has been captured adequately in E.U. SmPC Section 4.6 (Fertility, Pregnancy and Lactation).

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
History of alcohol or substance abuse in the past 2 years.	• To eliminate patients with risk factors for hepatic dysfunction. • To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	This criterion was not related to the safety of the patient population.
PIPF-016: Cigarette smoking within 3 months of Screening or unwilling to avoid tobacco products throughout the study.	Smoking induces the CYP1A2 isoenzyme. Patients should therefore be encouraged to discontinue the use of strong inducers of CYP1A2 and to stop smoking before and during treatment with pirfenidone.	No	This criterion was not related to the safety of the patient population.
History of any condition or habit associated with altered consciousness and a risk of aspiration in the past 2 years.	To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	Standard clinical trial exclusion criteria for safety reasons.
Family or personal history of long QT syndrome or/ ECG with QTc interval > 500 msec.	To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	This criterion was not related to the safety of the patient population.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Any of the following liver function test criteria above specified limits: Total bilirubin > 2.5 × ULN; aspartate or alanine aminotransferases (AST/SGOT or ALT/SGPT) > 1.5 × ULN; ALP > 2.0 × ULN.	• To eliminate patients with risk factors for hepatic dysfunction. • To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	Currently being monitored as an important identified risk. The information has been adequately captured in E.U. SmPC Section 4.2 (Posology and method of administration).
Patients are excluded if they receive the following therapies within 28 days prior to screening: • Investigational therapy defined as any drug that has not been approved for marketing for any indication in the country of the participating site.	To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	This criterion was not related to the safety of the patient population.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
• Any cytotoxic, immunosuppressive, cytokine modulating, or endothelin receptor antagonist agent including but not limited to: azathioprine, bosentan, corticosteroids (i.e., >15 mg/d of prednisolone or equivalent), cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotrienes, methotrexate, mycophenolate mofetil, sildenafil (daily), tetrathiomolybdate, TNF-α inhibitors, NAC, imatinib mesylate, IFN-γ1b), and TKI. • Concomitant medications being used for the treatment of IPF (including but not limited to): ACE-inhibitors, colchicine, warfarin, heparin, sildenafil, fluvoxamine and HMG-CoA reductase inhibitors. These drugs may be used if given for a non-IPF indication if there is no clinically acceptable alternative therapy for the same indication.			

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients previously treated with pirfenidone or nintedanib	To eliminate patients with IPF as already part of the approved indication	No	This criterion was not related to the safety of the patient population
Significant co-existent emphysema (extent greater than extent of fibrosis on HRCT within the last 12 months)	To eliminate patients coexisting emphysema as it can make evaluation of treatment effect difficult.	No	This criterion was not related to the safety of the patient population.
CrCl < 30 mL/min, calculated using the Cockcroft-Gault formula	• To eliminate patients with risk factors for renal dysfunction. • To minimize the potential risk to patients and to avoid confounding factors on the assessment of efficacy and safety of the study drug.	No	Esbriet should be used with caution in patients with moderate (CrCl 30–50 mL/min) to severe (CrCl < 30 mL/min) renal impairment. Esbriet has not been studied and is not recommended in patients with end-stage renal disease requiring dialysis [Esbriet CDS v10.0].

ACE = angiotensin-converting enzyme; CDS = Core Data Sheet; CrCl = creatinine clearance; FEV = forced expiratory volume; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; HbA1C = glycosylated hemoglobin; HRCT = high-resolution computed tomography; IFN-γ1b = interferon gamma 1b; IPF = idiopathic pulmonary fibrosis; NAC = N-acetylcysteine; RV = residual volume; SmPC = Summary of Product Characteristics; TKI = tyrosine kinase inhibitor; TNF-α = tumor necrosis factor-alpha; ULN = upper limit of normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAM

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 11 Exposure of Special Populations Included or Not in the Clinical Trial Development Program

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities	
Patients with hepatic impairment	Total: 12 Patients • Group 1 (Moderate liver cirrhosis: Child-Pugh Class B/Child-Pugh score of 7–9): 12
Patients with renal impairment	Total: 20 Patients • Mild renal impairment (CrCl >50 and ≤80): 6 • Moderate impairment (CrCl ≥30 and ≤50): 7 • Severe impairment(CrCl <30) : 7
Patients with cardiovascular impairment	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Immuno-compromised patients	Not included in the clinical development program.
Population with relevant different ethnic origin	Total: 623 Patients • Hispanic or Latino: 65 (10.4%) • Not Hispanic or Latino: 558 (89.6%)
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

Table 11 Exposure of Special Populations Included or Not in the Clinical Trial Development Program (cont.)

Type of special population	Exposure
Other	
Children :	Not included in the clinical development program.
Elderly: IPF generally occurs in patients aged 50 years or older.	Total: 1163 Patients • ≥ 65 years: 878 • ≥ 75 years: 285

CrCl = creatinine clearance, IPF = Idiopathic pulmonary fibrosis.

Source: NDA Safety update listing 2U, March 2014.

PART II: MODULE SV – POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method Used to Calculate Exposure

The methodology used for patient exposure calculation was as below:

- Patient equivalent: Total Volume / (Dose/day/patient x Compliance × Persistence × 365 days)
- *Patient Year: Total Pills / (7.2 pills × Persistence × 365 days)*

  Persistence refers to the percentage of time a patient stays on treatment in a 12 month period.
- Patient Year: Total Volume / (Dose/day/patient × Compliance × 365 days)

Data from commercial sales and Named Patient Programs (NPPs) have been used to calculate the cumulative patient exposure to Esbriet® from marketing experience.

The volume sold by Roche is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis). The sales data are provided on a monthly basis; therefore, the exposure is available from the International Birth Date (IBD, 28 February 2011) to the nearest point data lock point (DLP, i.e., *27* February 202*2* [Periodic Benefit-Risk Evaluation Report RDR *1113548*]).

- The cumulative exposure was estimated by adding the results of the interval exposure since IBD per Roche estimation methodology (see above)

The source for the persistence data is the Roche IPF market tracker. The IPF market tracker is a Roche commissioned primary market research project conducted in 5 E.U. Countries (Germany, Spain, France, Italy and U.K.).

SV.1.2 Exposure

As of February 202*2*, the estimated cumulative total exposure to Esbriet® from marketing experience is *306,149* patient-equivalent and *208,790* patient-years (see Table 12 and Table 13, respectively).

Table 12 Cumulative Exposure from Marketing Experience (Patient-Equivalent)

Patient Equivalent											
Source	**Indication**	**Sex**		**Age**				**Region**			
		Male	**Female**	**0 to ≤18 yrs**	**>18 to ≤65 yrs**	**>65 yrs**	**Unknown**	**EEA**	**U.S.**	**ROW**	**Total**
Commercial	**IPF**	*176,023*	*97,059*	0	*76,512*	*196,570*	0	*121,759*	*117,669*	*33,654*	*273,082*
NPP		*20,837*	*12,230*	0	*6,238*	*26,829*	0	*1,929*	*28,442*	*2,696*	*33,067*
Sub-total		*196,860*	*109,289*	0	*82,750*	*223,399*	0	*123,688*	*146,111*	*36,351*	*306,149*
Total		***306,149***		***306,149***				***306,149***			

DLP = data lock point; EEA = European Economic Area; IPF = idiopathic pulmonary fibrosis; NPP = Named Patient Program; PBRER = Periodic Benefit-Risk Evaluation Report; ROW = Rest of World; U.S. = United States.

Note: Exposure data in subgroups may not equal the overall totals due to rounding errors.

The Cumulative Exposure from Marketing Experience (Patient-Equivalent) is taken from latest PBRER DLP, *27* February 202*2* (RDR *1113548*).

Table 13 Cumulative Exposure from Marketing Experience (Patient-Years)

Patient Years											
Source	**Indication**	**Sex**		**Age**				**Region**			
		Male	**Female**	**0 to ≤18 yrs**	**>18 to ≤65 yrs**	**>65 yrs**	**Unknown**	**EEA**	**U.S.**	**ROW**	**Total**
Commercial	**IPF**	*122,293*	*66,837*	0	*56,113*	*133,017*	0	*96,109*	*67,368*	*25,654*	*189,130*
NPP		*12,362*	*7,298*	0	*3,959*	*15,700*	0	*1,828*	*15,184*	*2,647*	*19,659*
Sub-total		*134,655*	*74,135*	0	*60,073*	*148,717*	0	*97,937*	*82,552*	*28,301*	*208,790*
Total		***208,790***		***208,790***				***208,790***			

DLP = data lock point; EEA = European Economic Area; IPF = idiopathic pulmonary fibrosis; NPP = Named Patient Program; PBRER = Periodic Benefit-Risk Evaluation Report; ROW = Rest of World; U.S. = United States.

Note: Exposure data in subgroups may not equal the overall totals due to rounding errors.

The Cumulative Exposure from Marketing Experience (Patient-Equivalent) is taken from latest PBRER DLP 2*7* February 202*2* (RDR *1113548*).

PART II: MODULE SVI – ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The MAH is not aware of any evidence to suggest a potential for misuse or abuse and so this risk is thought to be very low.

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Severe skin reactions, previously classified as an important potential risk, is no longer included in the list of safety concerns in the RMP. Stevens-Johnson syndrome and toxic epidermal necrolysis have been included in Section 4.4 and Section 4.8 of the SmPC, based on the Pharmacovigilance Risk Assessment Committee (PRAC) Periodic Safety Update Report (PSUR) Assessment Report (procedure number EMEA/H/C/PSUSA/00002435/202102). The risk of severe skin reactions will be subject to routine pharmacovigilance and risk minimization measures and no additional pharmacovigilance activities are deemed necessary. The risk is therefore removed from the RMP as an important potential risk.

As requested by the PRAC in the assessment report for procedure number EMEA/H/C/002154/II/0074, the following safety concerns have been removed from the list of safety concerns in the RMP:

- *Gastrointestinal symptoms, previously classified as an important identified risk*
- *Risk of medication error in patients transferring between capsules and tablets, previously classified as an important potential risk*
- *Patients with QT prolongation*
- *Patients with underlying specific cardiac events, previously classified as missing information*

None of these safety concerns are subject to additional pharmacovigilance activities and no additional risk minimization measures are in place. The SmPC describes the routine risk minimization measures in place for Gastrointestinal symptoms, and these symptoms are well recognized and well-characterized. Following continued

post-marketing monitoring by the MAH, no safety signal has emerged for the other safety concerns. Therefore, it is considered at this stage of the product life cycle these safety concerns can be removed from the RMP. The MAH will continue to monitor such events via routine pharmacovigilance and present an evaluation of any newly emerging data via the appropriate regulatory channels.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Information on Important Identified Risks

The following section is based on data presented in the ISS RSU and describes 2 important patient subsets:

- The Randomized Patient Subset: pirfenidone 2403 mg/day (623 patients) and placebo (624 patients) in Studies PIPF-004, PIPF-006, and PIPF-016, totaling 1247 patients
- The Pirfenidone Patient Original Treatment Arm Subset: patients who received at least 1 dose of pirfenidone in Studies PIPF-004, PIPF-006, PIPF-016, as well as open-label Studies PIPF-002 and PIPF-012 (which only contained patients originally enrolled in Studies PIPF-004 and PIPF-006), totaling 1067 patients (2014 RSU Table 1.1-1U). This represents a subset of the overall Pirfenidone Patient Subset described in Part II, Module SIII (N = 1299).

Photosensitivity Reaction and Rash

MedDRA terms: Photosensitivity reaction, rash

Potential mechanism: Cutaneous photosensitivity is due to UV ray exposure after administration of this drug. It is transient and is alleviated by discontinuing administration or reducing the dose.

Evidence source(s) and strength of evidence: A series of 4 nonclinical studies have been conducted to evaluate the potential phototoxic effects of pirfenidone in the presence of UV light in guinea pigs. Some of these studies detected erythema of the skin in guinea pigs as well as irritation and inflammation histologically. However, the phototoxic effects on skin were mitigated by the use of sunscreens with SPF values of 50 or greater. In hairless mice treated with pirfenidone and exposed to UV, reversible mild acanthosis and mild single cell necrosis were observed in the epidermis of the auricle and the dorsal skin. There was no systemic toxicity. Incidence in patients has been derived from clinical studies in the E.U. and U.S.

Characterization of the Risk

Incidence/prevalence

No epidemiologic data estimating background incidence or prevalence of photosensitivity reactions or rash among patients with IPF were identified. Based on the placebo data from Studies PIPF-004, 006 and 016 (Phase III studies) with pirfenidone, 7/624 (1.1%) unexposed patients experienced photosensitivity reactions and 64/624 (10.3%) patients reported rash.

Frequency with 95 % CI

Pirfenidone Patient Original Treatment Arm Subset: frequency and 95% CI of Photosensitivity reaction and Rash:

- Photosensitivity reaction: 11.1% (9.2%–13.1%)
- Rash: 27.6% (25.0%–30.4%)
- Overall: 35.7% (32.8%–38.7%)

Source: Adapted from t_risks_95_ core_id.rtf Important Identified Risks.

Frequency in the Randomized, Blinded Trial Population

Photosensitivity

In the Randomized Patient Subset, photosensitivity reaction was reported for 9.3% of pirfenidone patients and 1.1% of placebo patients. In the pirfenidone group, 5 patients (0.8%) had Grade 3 events, 1 patient (0.2%) had a treatment-emergent serious adverse event (TESAE), and 4 patients (0.6%) discontinued treatment for a photosensitivity reaction; no patient had a Grade 4 event, was hospitalized, or died. In the placebo group, 1 patient (0.2%) had a Grade 3 event and 1 patient (0.2%) discontinued treatment because of a photosensitivity reaction; no patient had a Grade 4 event, a TESAE, was hospitalized, or died.

Rash

In the Randomized Patient Subset, rash was reported for 30.3% of pirfenidone patients and 10.3% of placebo patients. In the pirfenidone group, 4 patients (0.6%) had Grade 3 rash, 1 patient (0.2%) had a TESAE, and 8 patients (1.3%) discontinued treatment for a rash; no patient had a Grade 4 event, was hospitalized, or died. In the placebo group, 1 patient (0.2%) had a Grade 3 event; no patient had a Grade 4 event, a TESAE, was hospitalized, discontinued treatment, or died because of rash.

Frequency in Epidemiological Studies

No epidemiological studies were conducted.

Severity and Nature of Risk

Photosensitivity

In the Randomized Patient Subset, 5 (0.8%) of the 623 patients treated with pirfenidone 2403 mg/day reported a Grade 3 photosensitivity reaction. One (0.2%) of the 624 patients treated with placebo reported Grade 3 photosensitivity reaction. Half of the patients in the pirfenidone 2403 mg/day group who reported photosensitivity reaction first did so between Month 0 and 3. The majority of photosensitivity reactions in the Pirfenidone Patient Original Treatment Arm Subset (112/118, 95%) were Grades 1 or 2. Overall, no patient experienced Grade 4 photosensitivity reaction during pirfenidone treatment. The risk is potentially severe due to the nature of the possible long-term adverse effects arising from sunburn and skin damage.

Rash

In the Randomized Patient Subset, 4 (0.6%) of the 623 patients treated with pirfenidone 2403 mg/day reported a Grade 3 rash. One (0.2%) of the 624 patients treated with placebo reported a Grade 3 rash. In the majority of patients with rash in the Pirfenidone Patient Original Treatment Arm Subset (289/295, 98%), the severity was Grade 1 or Grade 2. Overall, no patient experienced a Grade 4 rash during pirfenidone treatment. Most patients in the pirfenidone 2403 mg/day group, who reported a rash first, did so between Month 0 and 6.

Seriousness/outcomes

In the Pirfenidone Patient Original Treatment Arm Subset, there were 381 patients (35.7%) with rash and/or photosensitivity reaction; these events tended to occur within the first 6 months of treatment (276/381, 72%).

Impact on Quality of Life

Patients treated with pirfenidone who experience a photosensitivity reaction may require treatment with topical corticosteroids and may need to reduce the dose or stop pirfenidone. Patients taking pirfenidone should take measures to avoid or protect against (sun blocks, clothing) sun exposure.

Risk Factors and Risk Groups

No specific groups or factors indicating increased risk of photosensitivity reaction or rash have been identified for either patients with IPF or those treated with pirfenidone.

Photosensitivity

In the Randomized Patient Subset, approximately 9 times the percentage of patients treated with pirfenidone 2403 mg/day compared with placebo reported a photosensitivity reaction. Sex, age, race, and baseline IPF severity did not appear to have an effect on photosensitivity reaction.

Rash

In the Randomized Patient Subset, approximately 3 times the percentage of patients treated with pirfenidone 2403 mg/day compared with placebo reported a rash. There was a suggestion of a race effect. In the pirfenidone 2403 mg/day group, after subtracting the placebo effect, 12.8% more white patients than non-white patients reported rash; however, sex, age, and baseline IPF severity did not appear to have an effect. In the general population, risk factors for photosensitivity reactions include prolonged exposure to the sun and UV rays; diseases such as dermatomyositis and lupus erythematosus; and certain drugs and drug classes (e.g., antibiotics [quinolones, tetracyclines, sulfonamides]), non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, chemotherapeutics agents and retinoids.

Preventability

Direct exposure to strong UV radiation should be avoided during treatment with pirfenidone. Patients should be cautioned to use sun block and appropriate protective clothing to minimize sun exposure.

In Section 4.4 of the SmPC, special warnings and precautions for use of Esbriet have been stated to avoid photosensitivity reaction and rash. It is advised that exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with Esbriet. Patients should be instructed to use a sunblock daily, to wear clothing that protects against sun exposure, and to avoid other medications known to cause photosensitivity.

A statement has also been included in Section 4.2 of the SmPC that dose adjustment or temporary treatment discontinuation may be necessary in patients who experience a mild to severe photosensitivity reaction or rash.

A Safety Checklist about monitoring and management of photosensitivity reaction and rash was made available via distribution at the time of each formulation launch to all local medical staff involved in managing patients with IPF. It requests reporting of all clinically-significant adverse drug reactions (ADR) of photosensitivity reaction and rash to the MAH where an association is suspected. Given that the incidence of photosensitivity reaction is increased in early summer, particular attention should be paid to preventive measures during those months.

Impact on the Benefit-Risk Balance of the Product

The impact of photosensitivity reaction and rash on the benefit-risk balance of pirfenidone is considered low since the adverse events (AEs) are typically non-serious, transient, and manageable per the label. The risk minimization activities consisting of educational material/label, mitigate both risk severity and early discontinuation of pirfenidone. In consideration of the benefit conferred by the drug, and the ability to manage the risk, the impact on the benefit-risk balance is low.

Public Health Impact

The potential public health impact of photosensitivity reaction and rash is low based on the typically non-serious, transient, and manageable nature of these AEs.

Drug-Induced Liver Injury (DILI)

MedDRA terms: Standardised MedDRA Query (SMQ) drug-related hepatic disorders – severe events only (narrow) and related sub-SMQs.

Potential mechanism: Unknown

Evidence source(s) and strength of evidence: Incidence in patients has been derived from clinical studies in the E.U. and U.S. and estimates of post-marketing patient exposure

Characterization of the Risk

Incidence/prevalence

Drug-induced liver injury has an estimated annual incidence between 10 and 15 per 10,000 to 100,000 persons exposed to prescription medications. *The prevalence and cause of DILI varies geographically (Hassan and Fontana 2018). Drug-induced liver injury accounts for approximately 10% of all cases of acute hepatitis (Zimmerman 2000), is the cause of acute jaundice in 50% of patients who present with new jaundice, and accounts for up to half of the cases of acute liver failure in Western countries (Larrey 2002; Ostapowicz et al. 2002; Sgro et al. 2002; Larson et al. 2005; Hussaini et al. 2007; Wei et al. 2007; Reuben et al. 2010).*

There were no reports of DILI during the pivotal clinical trials. Thus, its frequency has been estimated based on the guidance provided with “A Guideline on Summary of Product Characteristics (SmPC), Revision 2” released by the European Commission in September 2009. Considering that 623 patients have been enrolled in Esbriet pivotal trials and that the upper limit of the 95% CI is not higher than 3/623, then the upper limit of the 95% CI for the point estimate is 1/207 or less and the resulting frequency category is "uncommon", based on the worst value of the point estimate.

Clinically silent liver enzyme abnormalities have been detected during clinical development, and are well-described in the E.U. SmPC (Section 4.4). In the pooled pivotal Studies PIPF-004, -006 and -016, the placebo group included 9/624 (1.4%) patients with reported ALT increase and 9/624 (1.4%) patients with reported AST increase (Section 2.2 and Table 7 of Drug Safety Report [DSR] 1097072).

Frequency with 95 % CI

Pirfenidone Patient Original Treatment Arm Subset: frequency and 95% CI of Abnormal liver function tests (LFTs), Increased ALT and AST Levels, Total Serum Bilirubin Increased in Combination with Increases of ALT and AST:

- ALT increased: 3.0% (2.1%–4.2%)
- AST increased: 2.6% (1.8%–3.8%)
- Blood bilirubin increased: 0.3% (0.1%–0.8%)
- LFT abnormal: 1.8% (1.1%–2.8%)
- Gamma-glutamyltransferase increased: 5.7% (4.4%–7.3%)
- Hepatic enzyme increased: 1.5% (0.9%–2.4%)
- Hepatic function abnormal: 0.1% (0.0%–0.5%)
- Hyperbilirubinemia: 0.2% (0.0%–0.7%)
- Transaminases increased: 0.8% (0.4%–1.6%)
- Overall: 13.8% (11.8%–16.0%)

Source: Adapted from t_risks_95_ core_id.rtf Important Identified Risks.

Severity and Nature of Risk

A cumulative assessment of all the available evidence concerning severe hepatotoxicity in patients treated with pirfenidone was performed in 2019 (DLP: 30 June 2019; DSR 1097072). This included the review of nonclinical, clinical studies, literature data and post-marketing reports, plus a retrospective cohort study of a claim database (PharmMetrics™). No evidence of liver damage following exposure to pirfenidone was found during the review of toxicology studies data. The review of clinical trial data showed an increased cumulative incidence of hepatic TEAEs with pirfenidone versus the control arm (placebo). The majority of these TEAEs (9.5% pirfenidone vs. 4.3% placebo) were laboratory abnormalities without clinical consequences (RSU 2014).

Cumulatively, as of the DLP date of the DSR (i.e., 30 June 2019), 383 cases reporting 418 events were retrieved from the Roche global safety database using MedDRA SMQ drug-related hepatic disorders – severe events only (narrow) and related sub SMQs. In line with the known epidemiology of IPF, the majority of these cases were reported in elderly patients (62.4%) and included manifestation of DILI such as liver disorders, liver injury, hepatotoxicity, hepatocellular injury, and liver failure. In 24 of the 383 cases

(6.2%), the reported event led to a fatal outcome. Reports providing sufficient information were assessed for causality via the Roussel Uclaf Causality Assessment Method (RUCAM) score, an algorithm widely used to assess the causal relationship between medicines and DILI; this was possible in 22 of the 383 cases (5.7%). Two of these 22 cases (9.1%) recently published in the literature (Verma et al. 2017; Benesic et al. 2019) had a RUCAM score of 6–8 indicating a highly probable causal association with the use of pirfenidone, whereas 3 cases (13.6%) had a RUCAM score of 3–5 implying a probable causal association. The remaining 361 cases (94.3%) where a RUCAM score could not be assessed were reviewed based on the available evidence and categorized as probable causal relationship (1, 0.3%), questionable causal relationship due to alternative and more likely etiologies (113, 31.3%) and cases presenting with insufficient information (247, 68.4%).

Based on the above evidence, it is justified to conclude that pirfenidone is causally associated with clinical manifestations of DILI, including rare cases with fatal outcome, possibly caused by idiosyncratic reactions to pirfenidone. Subsequently, DILI was added as important identified risk to the E.U. RMP.

Impact on Quality of Life

Drug-induced liver injury can develop following the use of many prescriptions and over-the-counter drugs through a variety of mechanisms, and can resemble almost all known types of acute, subacute, and chronic liver disease (Chalasani et al. 2014). Therefore, the impact on quality of life varies greatly, ranging from negligible in case of clinically silent laboratory abnormalities to severe in case of serious manifestations such as acute liver failure.

Risk Factors and Risk Groups

Subgroup analyses of specific liver-related laboratory outcomes by sex, age and baseline IPF severity was not possible as there were too few patients in these subgroups to draw meaningful conclusions. Risk groups or risk factors are dependent on the nature of the liver disorder although non-specific factors for all forms of hepatic dysfunction such as alcohol abuse are well-recognized.

Preventability

Esbriet (pirfenidone) should be used with caution in patients with preexisting mild to moderate hepatic impairment. Esbriet should not be used in patients with severe or end stage liver disease. Because pirfenidone is metabolized by the liver, dosing of pirfenidone and/or other drugs metabolized in the liver may require adjustment upon starting or stopping concomitant therapy.

In the setting of regular LFT monitoring and a dose-modification plan in the Phase III clinical studies, hepatotoxicity occurred infrequently, was manageable, and was reversible. Most patients normalized or improved their laboratory abnormalities over time, generally without permanent dose modifications. Rarely have these elevations been associated with concomitant elevations in bilirubin. However, clinical manifestations of DILI including cases with fatal outcome –possibly caused by idiosyncratic reactions to pirfenidone – have been reported post-marketing in rare instances (DSR 1097072).

The SmPC Section 4.4 (Special Warnings and Precautions), provides detailed recommendations to monitor LFTs prior to the initiation of the treatment and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter. In addition, LFTs should be promptly measured in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. It has also been recommended that in case of ALT and/or AST elevations >3 to <5 ×upper limit of normal (ULN) without bilirubin elevation after starting pirfenidone therapy, other causes should be excluded, and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered. If clinically appropriate, the dose of pirfenidone should be reduced or interrupted (e.g., until LFTs are within normal limits) with subsequent re-escalation to the recommended daily dose if tolerated. Pirfenidone should be discontinued and the patient should not be rechallenged if a patient exhibits an AST and/or ALT elevation >3 to <5 ×ULN accompanied by hyperbilirubinemia or clinical signs or symptoms indicative of liver injury, or if a patient exhibits an aminotransferase elevation to ≥5 ×ULN.

In Section 4.3 of the SmPC, the use of pirfenidone is contraindicated in patients with severe hepatic impairment or end stage liver disease.

Potential risk factors for hepatic dysfunction, in general, are known and awareness of these, coupled with advice in the SmPC that pirfenidone should be used with caution in patients with preexisting mild to moderate hepatic impairment will help minimize the risk from increased exposure to pirfenidone. A Safety Checklist about monitoring and management of hepatic-related events, including asymptomatic abnormal levels of ALT/ AST was made available to be distributed at the time of launch to all local medical staff involved in managing patients with IPF. It requests reporting of all clinically-significant ADRs of liver-related abnormalities to the MAH.

Impact on the Benefit-Risk Balance of the Product

The impact of DILI is considered low in most of the cases, characterized by asymptomatic incidental lab findings, and manageable per the label. There were no reports of DILI during the pivotal clinical trials and approximately half of the reports received post-marketing recovered without sequelae. The risk minimization activities

consisting of educational material/label, including recommendation of baseline and periodic laboratory tests, enables early identification and mitigation of the risk.
In consideration of the benefit conferred by the drug, the rarity of DILI reports, and the ability to manage the risk by monitoring LFTs and reducing or discontinuing treatment in case of abnormal values, the overall impact on the benefit-risk balance is deemed acceptable.

Public Health Impact

The potential public health impact of DILI is deemed acceptable in consideration of the benefit conferred by the drug, the rarity of DILI and the ability to manage the risk by monitoring LFTs and reducing or discontinuing treatment in case of abnormal values.

SVII.3.2 Presentation of the Missing Information

Information on Missing Information

No missing information is currently identified for Esbriet.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 14 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Photosensitivity reaction and rash • DILI
Important potential risks	None
Missing information	None

DILI = drug-induced liver injury.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

Other forms of routine pharmacovigilance activities for:

- Photosensitivity Reaction and Rash
- DILI

A guided questionnaire is used to collect DILI case details and information about adherence to liver monitoring.

A cumulative medical review of spontaneous reports is carried out at least quarterly. The outcome of these reviews is included in the Periodic Benefit-Risk Evaluation Reports (PBRER).

Reporting of any findings to regulatory authorities is done as required, based on the nature and strength of the evidence and its impact on benefit risk assessment.

Although pregnancy is a rare occurrence in this elderly patient population, any pregnancy reports will be followed up via the Roche standard pregnancy follow-up process. This was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered by the MAH to be sufficient to obtain and analyze relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No post-authorization efficacy studies were required as a condition of the Marketing Authorization and no other imposed post-authorization efficacy studies are planned or ongoing.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 15 Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Photosensitivity Reaction and Rash	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) ***Patient Information Leaflet:*** *Section 2 What you need to know before you take Esbriet – Warnings and Precautions* *Section 3 How to take Esbriet – Dose reduction due to side effects* *Section 4 Possible side effects*

Table 15 Description of Routine Risk Minimization Measures by Safety Concern (cont.)

Safety Concern	Routine Risk Minimization Activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: Exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with pirfenidone. Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded to use a sunblock daily and to avoid exposure to the sun, to wear clothing that protects against sun exposure, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to report symptoms of photosensitivity reaction or rash to their physician. Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice (see Section 4.4). Once the rash has resolved, pirfenidone may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician. Severe photosensitivity reactions are uncommon. Dose adjustments or temporary treatment discontinuation may be necessary in mild to severe cases of photosensitivity reaction or rash (see Section 4.2). This has been adequately captured in Section 4.4 of E.U. SmPC. **Other routine risk minimization measures beyond the Product Information:** **Pack size:** None **Medicine's legal status:** Pirfenidone is a prescription only medicine.
DILI	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) ***Patient Information Leaflet:*** *Section 2 What you need to know before you take Esbriet – Warnings and Precautions* *Section 3 How to take Esbriet – Dose reduction due to side effects* *Section 4 Possible side effects* **Routine risk minimization activities recommending specific clinical measures to address the risk:** Hepatic function

	Elevated transaminases have been commonly reported in patients treated with pirfenidone. Liver function tests (ALT, AST and bilirubin) should be performed prior to the initiation of treatment with pirfenidone, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter (see Section 4.8 of the Esbriet SmPC).
Safety Concern	**Routine Risk Minimization Activities**
	If a patient exhibits an aminotransferase elevation >3 to $<5 \times$ ULN without bilirubin elevation and without symptoms or signs of DILI after starting pirfenidone therapy, other causes should be excluded, and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered. If clinically appropriate, the dose of pirfenidone should be reduced or interrupted. Once liver function tests are within normal limits pirfenidone may be re-escalated to the recommended daily dose if tolerated. <u>DILI</u> Uncommonly, elevations in AST and ALT were associated with concomitant bilirubin increases. Cases of severe DILI, including isolated cases with fatal outcome, have been reported post-marketing (see Section 4.8 of the Esbriet SmPC). In addition to the recommended regular monitoring of liver function tests, prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. If a patient exhibits an aminotransferase elevation >3 to $<5 \times$ ULN accompanied by hyperbilirubinaemia or clinical signs or symptoms indicative of liver injury, pirfenidone should be permanently discontinued and the patient should not be rechallenged. If a patient exhibits an aminotransferase elevation to $\geq 5 \times$ ULN, pirfenidone should be permanently discontinued and the patient should not be rechallenged. <u>Hepatic impairment</u> In subjects with moderate hepatic impairment (i.e., Child-Pugh Class B), pirfenidone exposure was increased by 60%. Pirfenidone should be used with caution in patients with pre-existing mild to moderate hepatic impairment (i.e., Child-Pugh Class A and B) given the potential for increased pirfenidone exposure. Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see Sections 4.5 and 5.2 of the Esbriet SmPC). Pirfenidone has not been studied in individuals with severe hepatic impairment and Esbriet must not be used in patients with severe hepatic impairment (see Section 4.3 of the Esbriet SmPC). **Other routine risk minimization measures beyond the Product Information:** **Pack size:** None **Medicine's legal status:** pirfenidone is a prescription only medicine.

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

Table 16 Additional Risk Minimization Measures

Photosensitivity Reaction and Rash	
Additional Risk Minimization Measure	Safety Checklist
Objectives	To Intensify communication and medical and patient education around photosensitivity reaction and rash with measures to avoid exposure to sun and other UV sources and risk of photosensitivity reactions.
Rationale for the additional risk minimization activity	To prevent clinically significant ADRs of photosensitivity reaction and rash where an association is suspected and to better clarify the nature of the rash, and identify specific risk factors if the event manifests.
Target audience and planned distribution path	All local medical staff involved in managing patients with IPF.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness will be measured: 1. Monitor distribution metrics of checklist at the time of local tablet launch. 2. Monitor against increasing trends in worldwide and regional (E.U., U.S., ROW) exposure adjusted reporting rates and document in the PBRER. Criteria for judging the success: 1. If metrics of educational materials distribution at PBRER time are not adequate, Safety Science will work with the Local Safety Unit to identify reasons and address with remediation. 2. If an increase trend in worldwide or regional exposure adjusted reporting rates is identified, a root-cause analysis will be conducted assessing the reports for the geography at issue to determine risk factors and efficacy of education. Further reinforcement and education on the need for preventing/reducing exposure to UV light by the patient may be conducted to make prescribers and patients aware of these factors. In addition, further reinforcement might be proposed in the SmPC and PL if there was an aggregate signal. Planned dates for assessment: With PBRER

Table 16 Additional Risk Minimization Measures (cont.)

DILI	
Additional Risk Minimization Measure	Safety Checklist
Objectives	To enhance communication of the risk and related recommendations to minimize it.
Rationale for the additional risk minimization activity	To educate prescribing physicians on the need for liver enzyme monitoring and what actions to take with regard to pirfenidone dose management and to better clarify the nature of the hepatic abnormalities, and identify specific risk factors if the event manifests.
Target audience and planned distribution path	All local medical staff involved in managing patients with IPF.
Plans for evaluating the effectiveness of the interventions and criteria for success	<u>How effectiveness will be measured:</u> 1. Monitor distribution metrics of checklist at the time of local tablet launch. 2. Monitor against increasing trends in worldwide and regional (E.U., U.S., ROW) exposure adjusted reporting rates and document in the PBRER. 3. Adjudication by DILI experts of serious reports suggestive of association with pirfenidone. Periodic monitoring of exposure-adjusted reporting rates per 10,000 PYs of exposure, both overall and for the serious event subset. <u>Criteria for judging the success:</u> 1. If metrics of educational materials distribution at PBRER time are not adequate, Clinical Safety will work with the Local Safety Unit to identify reasons and address with remediation. 2. If an increase trend in worldwide or regional exposure adjusted reporting rates is identified, a root-cause analysis will be conducted assessing the reports for the geography at issue to determine risk factors and efficacy of education. Further reinforcement and education on the need for monitoring of liver enzymes and reducing the dose will be conducted to make prescribers and patients aware of these factors. In addition, further reinforcement might be proposed in the SmPC and PL if there was an aggregate signal. Planned dates for assessment: With PBRER

E.U. = European Union; HCP = Healthcare Provider; PBRER = Periodic Benefit-Risk Evaluation Report; PL = Package Leaflet; ROW = Rest of the World; SmPC = Summary of Product Characteristics; UILD = unclassifiable interstitial lung disease; U.S. = United States; UV = ultraviolent.

Removal of Additional Risk-Minimization Activity of Dear Healthcare Professional Letter & Dear Investigator Letter

Rationale for the removal of the Dear Healthcare Professional (DHPC) and Dear Investigator Letter (DIL) for Clinically Relevant DILI:

- The DHPC letter and the DIL for clinically relevant DILI – were a point-in-time action to advise clinical trial investigators and prescribers about the new DILI information

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 17 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Photosensitivity reaction and rash	**Routine risk minimization measures:** ***Routine risk communication:*** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) ***Patient Information Leaflet:*** *Section 2 What you need to know before you take Esbriet – Warnings and Precautions* *Section 3 How to take Esbriet – Dose reduction due to side effects* *Section 4 Possible side effects* **Routine risk minimization activities recommending specific clinical measures to address the risk:** Exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with pirfenidone. Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded to use a sunblock daily and to avoid exposure to the sun, to wear clothing that protects against sun exposure, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to report symptoms of photosensitivity reaction or rash to their physician. Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice (see Section 4.4). Once the rash has resolved, pirfenidone may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician. Severe photosensitivity reactions are uncommon.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** A cumulative medical review of spontaneous reports is carried out at least quarterly. The outcome of these reviews is included in the PBRERs. Reporting of any findings to regulatory authorities is done as required, based on the nature and strength of the evidence and its impact on benefit risk assessment. **Additional pharmacovigilance activities**: None

Table 17 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (cont.)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Dose adjustments or temporary treatment discontinuation may be necessary in mild to severe cases of photosensitivity reaction or rash (see Section 4.2). This has been adequately captured in Section 4.4 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** **Pack size:** None **Medicine's legal status: P**irfenidone is a prescription only medicine. **Additional risk minimization measures:** Safety Checklist: A Safety Checklist about monitoring and management of photosensitivity reaction and rash was made available to be distributed at the time of initial launch and with launch of any new formulation to all local medical staff involved in managing patients with IPF. It requests reporting of all clinically-significant ADRs of photosensitivity reaction and rash to the MAH, where an association is suspected.	
DILI	**Routine risk minimization measures:** ***Routine risk communication:*** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) ***Patient Information Leaflet:*** *Section 2 What you need to know before you take Esbriet – Warnings and Precautions* *Section 3 How to take Esbriet – Dose reduction due to side effects* *Section 4 Possible side effects*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** A Guided Questionnaire will be used to follow-up incoming reports of DILI. A cumulative medical review of spontaneous reports is carried out at least quarterly. The outcome of these reviews is included in the PBRERs. Reporting of any findings to regulatory

Table 17 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (cont.)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: Hepatic function Elevated transaminases have been commonly reported in patients treated with pirfenidone. Liver function tests (ALT, AST and bilirubin) should be performed prior to the initiation of treatment with pirfenidone, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter (see Section 4.8 of the Esbriet SmPC). If a patient exhibits an aminotransferase elevation >3 to $<5\times$ ULN without bilirubin elevation and without symptoms or signs of DILI after starting pirfenidone therapy, other causes should be excluded, and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered. If clinically appropriate, the dose of pirfenidone should be reduced or interrupted. Once liver function tests are within normal limits pirfenidone may be re-escalated to the recommended daily dose if tolerated. DILI Uncommonly, elevations in AST and ALT were associated with concomitant bilirubin increases. Cases of severe DILI, including isolated cases with fatal outcome, have been reported post-marketing (see Section 4.8 of the Esbriet SmPC). In addition to the recommended regular monitoring of liver function tests, prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. If a patient exhibits an aminotransferase elevation >3 to $<5\times$ ULN accompanied by hyperbilirubinaemia or clinical signs or symptoms indicative of liver injury, pirfenidone should be permanently discontinued and the patient should not be rechallenged. If a patient exhibits an aminotransferase elevation to $\geq 5\times$ ULN, pirfenidone should be permanently discontinued and the patient should not be rechallenged.	authorities is done as required, based on the nature and strength of the evidence and its impact on benefit risk assessment. **Additional pharmacovigilance activities:** None

Table 17 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (cont.)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Hepatic impairment In subjects with moderate hepatic impairment (i.e., Child-Pugh Class B), pirfenidone exposure was increased by 60%. Pirfenidone should be used with caution in patients with preexisting mild to moderate hepatic impairment (i.e., Child-Pugh Class A and B) given the potential for increased pirfenidone exposure. Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see Sections 4.5 and 5.2 of the Esbriet SmPC). Pirfenidone has not been studied in individuals with severe hepatic impairment and pirfenidone must not be used in patients with severe hepatic impairment (see Section 4.3 of the Esbriet SmPC). **Other risk minimization measures beyond the Product Information:** **Pack size**: None **Medicine's legal status:** Pirfenidone is a prescription only medicine. **Additional risk minimization measures:** Safety Checklist: A Safety Checklist about monitoring and management of DILI is to be distributed to all local medical staff involved in managing patients with IPF, and may be re-distributed in case of further updates or launch of new formulations. It requests HCPs to report all clinically-significant ADRs of liver-related abnormalities to the MAH.	

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ESBRIET (PIRFENIDONE)

This is a summary of the Risk Management Plan (RMP) for Esbriet. The RMP details important risks of Esbriet, how these risks can be minimized, and how more information will be obtained about Esbriet risks and uncertainties (missing information).

Esbriet's SmPC and its Package Leaflet give essential information to healthcare professionals and patients on how Esbriet should be used.

This summary of the RMP for Esbriet 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 Esbriet RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Esbriet is authorized for the treatment of IPF. It contains pirfenidone as the active substance and it is given by oral administration.

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

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

Measures to minimize 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 authorized 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 minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Esbriet, these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

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

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Esbriet are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. 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 Esbriet. 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	• Photosensitivity reaction and rash • DILI
Important potential risks	None
Missing information	None

DILI = drug-induced liver injury.

II.B SUMMARY OF IMPORTANT RISKS

Important Identified Risk: Photosensitivity Reaction and Rash	
Evidence for linking the risk to the medicine	A series of 4 nonclinical studies have been conducted to evaluate the potential phototoxic effects of pirfenidone in the presence of UV light in guinea pigs. Some of these studies detected erythema of the skin in guinea pigs as well as irritation and inflammation histologically. However, the phototoxic effects on skin were mitigated by the use of sunscreens with SPF values of 50 or greater. In hairless mice treated with pirfenidone and exposed to UV, reversible mild acanthosis and mild single cell necrosis were observed in the epidermis of the auricle and the dorsal skin. There was no systemic toxicity. Incidence in patients has been derived from clinical studies in the E.U. and U.S.
Risk factors and risk groups	No specific groups or factors indicating increased risk of photosensitivity reaction or rash have been identified for either patients with IPF or those treated with pirfenidone. *Photosensitivity*: In the Updated Randomized Patient Subset, approximately 9 times the percentage of patients treated with pirfenidone 2403 mg/day compared with placebo reported a photosensitivity reaction. Sex, age, race, and baseline IPF severity did not appear to have an effect on photosensitivity reaction.

Important Identified Risk: Photosensitivity Reaction and Rash	
	Rash: In the Updated Randomized Patient Subset, approximately 3 times the percentage of patients treated with pirfenidone 2403 mg/day compared with placebo reported a rash. There was a suggestion of a race effect. In the pirfenidone 2403 mg/day group, after subtracting the placebo effect, 12.8% more white patients than non-white patients reported rash; however, sex, age, and baseline IPF severity did not appear to have an effect. In the general population, risk factors for photosensitivity reactions include prolonged exposure to the sun and UV rays; diseases such as dermatomyositis and lupus erythematosus; and certain drugs and drug classes (e.g., antibiotics [quinolones, tetracyclines, sulfonamides]), NSAIDs, diuretics, chemotherapeutics agents and retinoids.
Risk minimization measures	**Routine risk minimization measures:** ***Routine risk communication*:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) ***Patient Information Leaflet:*** *Section 2 What you need to know before you take Esbriet – Warnings and Precautions* *Section 3 How to take Esbriet – Dose reduction due to side effects* *Section 4 Possible side effects* **Routine risk minimization activities recommending specific clinical measures to address the risk:** Exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with Esbriet. Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded to use a sunblock daily and to avoid exposure to the sun, to wear clothing that protects against sun exposure, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to report symptoms of photosensitivity reaction or rash to their physician. Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice (see Section 4.4 of the Esbriet SmPC). Once the rash has resolved, Esbriet may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician. Severe photosensitivity reactions are uncommon. Dose adjustments or temporary treatment discontinuation may be necessary in mild to severe cases of photosensitivity reaction or rash (see Section 4.2). This has been adequately captured in Section 4.4 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Esbriet is a prescription only medicine. **Additional risk minimization measures:**

Important Identified Risk: Photosensitivity Reaction and Rash	
	Safety Checklist: A Safety Checklist about monitoring and management of photosensitivity reaction and rash was made available to be distributed at the time of launch to all local medical staff involved in managing patients with IPF. It requests reporting of all clinically-significant ADRs of photosensitivity reaction and rash to the MAH, where an association is suspected.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

ADRs = adverse drug reactions; E.U. = European Union; IPF = idiopathic pulmonary fibrosis; MAH = Marketing Authorization Holder; NSAIDs = non-steroidal anti-inflammatory drugs; PASS = Post-Authorization Safety Study; SmPC = Summary of Product Characteristics; ULN = upper limit of normal; U.S. = United States, UV = Ultra Violet; SPF = Sun protecting factor

Important Identified Risk: DILI	
Evidence for linking the risk to the medicine	Incidence in patients has been derived from clinical studies in the E.U. and U.S. and approximations of post-marketing patient exposure.
Risk factors and risk groups	Subgroup analyses of specific liver-related laboratory outcomes in the pooled safety analyses, in relation to the effects of sex, age and baseline IPF severity was not possible as there were too few patients in these subgroups to draw meaningful conclusions. Risk groups or risk factors are dependent on the nature of the liver disorder although non-specific factors for all forms of hepatic dysfunction such as alcohol abuse are well-recognized.
Risk minimization measures	**Routine risk minimization measures:** ***Routine risk communication*:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) ***Patient Information Leaflet:*** *Section 2 What you need to know before you take Esbriet – Warnings and Precautions* *Section 3 How to take Esbriet – Dose reduction due to side effects* *Section 4 Possible side effects* **Routine risk minimization activities recommending specific clinical measures to address the risk**: Hepatic function

Important Identified Risk: DILI	
	Elevated transaminases have been commonly reported in patients treated with Esbriet. Liver function tests (ALT, AST and bilirubin) should be performed prior to the initiation of treatment with Esbriet, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter (see Section 4.8 of the Esbriet SmPC). If a patient exhibits an aminotransferase elevation >3 to $<5 \times$ ULN without bilirubin elevation and without symptoms or signs DILI after starting Esbriet therapy, other causes should be excluded, and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered. If clinically appropriate, the dose of Esbriet should be reduced or interrupted. Once liver function tests are within normal limits Esbriet may be re-escalated to the recommended daily dose if tolerated. <u>DILI</u> Uncommonly, elevations in AST and ALT were associated with concomitant bilirubin increases. Cases of severe DILI, including isolated cases with fatal outcome, have been reported post-marketing (see Section 4.8 of the Esbriet SmPC). In addition to the recommended regular monitoring of liver function tests, prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. If a patient exhibits an aminotransferase elevation >3 to $<5 \times$ ULN accompanied by hyperbilirubinaemia or clinical signs or symptoms indicative of liver injury, Esbriet should be permanently discontinued and the patient should not be rechallenged. If a patient exhibits an aminotransferase elevation to $\geq 5 \times$ ULN, Esbriet should be permanently discontinued and the patient should not be rechallenged. <u>Hepatic impairment</u> In subjects with moderate hepatic impairment (i.e., Child-Pugh Class B), pirfenidone exposure was increased by 60%. Esbriet should be used with caution in patients with preexisting mild to moderate hepatic impairment (i.e., Child-Pugh Class A and B) given the potential for increased pirfenidone exposure. Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see Sections 4.5 and 5.2 of the Esbriet SmPC). Esbriet has not been studied in individuals with severe hepatic impairment and Esbriet must not be used in patients with severe hepatic impairment (see Section 4.3 of the Esbriet SmPC). **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Esbriet is a prescription only medicine. **Additional risk minimization measures:** <u>Safety Checklist:</u>

Important Identified Risk: DILI	
	A Safety Checklist about monitoring and management of DILI is to be distributed to all local medical staff involved in managing patients with IPF, and may be redistributed in case of further updates or launch of new formulations. It requests HCPs to report all clinically-significant ADRs of liver-related abnormalities to the MAH.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

ADRs = adverse drug reactions; DILI = drug-induced liver injury; E.U. = European Union; HCP = Healthcare Professional; IPF = idiopathic pulmonary fibrosis; MAH = Marketing Authorization Holder; PASS = Post-Authorization Safety Study; RMM = risk minimization measure; SmPC = Summary of Product Characteristics; ULN = upper limit of normal; U.S. = United States.

II.C POST-AUTHORISATION DEVELOPMENT PLAN

II.C.1 Studies Which Are Conditions of the Marketing Authorization

There are no studies which are a condition of the marketing authorization or a specific obligation for Esbriet.

II.C.2 Other Studies in Post-Authorization Development Plan

There are no studies required for Esbriet.

ANNEX 1

EUDRAVIGILANCE INTERFACE

ANNEX 1

EUDRAVIGILANCE INTERFACE

Not Applicable

ANNEX 2

TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAM

ANNEX 2

TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAM

Not Applicable

ANNEX 3

PROTOCOLS FOR PROPOSED, ONGOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

ANNEX 3

PROTOCOLS FOR PROPOSED, ONGOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Not Applicable

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of Contents

Guided Questionnaire for the Assessment of Drug-Induced Liver Injury (DILI)

Roche

GUIDED QUESTIONNAIRE FOR ASSESSMENT OF DILI

AER:		Local Case ID:	
Site No:	☐ Not applicable	Patient Date of Birth (dd-MMM-yyyy):	
Patient ID/Initials:		Race:	☐ Caucasian ☐ Black ☐ Asian ☐ American Indian or Alaska Native ☐ Other (specify): _____
Patient Gender:	☐ M ☐ F	BMI (body weight (kg)/height (meter)^2:	

1. Roche Product(s) Dose Information

Product name	**Dose and Units**	**Frequency**	**Route**	**Dosage form**
Start date[1,2]		**Last dose date[1,3] prior to AE**		**Ongoing** ☐

How was Drug Regimen altered in response to the event?

Not altered	☐		
Altered due to AE	☐	*Specify below*	
Reduced	☐	**Date[1]**	
		New dose (units)	
Temporally interrupted	☐	**Stopped date[1]**	
		Restart date[1]	
Permanently discontinued	☐	**Date[1]**	
Rechallenge	☐	**Date[1]**	

1. ***All dates must be reported as dd-MMM-yyyy***
2. ***For an intermittent dosing regimen (e.g., cyclic therapy), if the event occurred between two cycles, enter the start date as the start date of first administration of the first cycle.***
3. ***For a dose escalation regimen, enter the dose at the time of the event. This date is of particular importance for intermittent dosing regimens (e.g., cyclic therapy).***

Roche Product(s) Dose Information (cont.)

Product name	Dose and Units	Frequency	Route	Dosage form
Start date[1,2]		**Last dose date[1,3] prior to AE**		**Ongoing** ☐

How was Drug Regimen altered in response to the event?

Not altered	☐		
Altered due to AE	☐	*Specify below*	
Reduced	☐	**Date[1]**	
		New dose (units)	
Temporally interrupted	☐	**Stopped date[1]**	
		Restart date[1]	
Permanently discontinued	☐	**Date[1]**	
Rechallenge	☐	**Date[1]**	

1. *All dates must be reported as dd-MMM-yyyy*
2. *For an intermittent dosing regimen (e.g., cyclic therapy), if the event occurred between two cycles, enter the start date as the start date of first administration of the first cycle.*
3. *For a dose escalation regimen, enter the dose at the time of the event. This date is of particular importance for intermittent dosing regimens (e.g., cyclic therapy).*

Product name	Dose and Units	Frequency	Route	Dosage form
Start date[1,2]		**Last dose date[1,3] prior to AE**		**Ongoing** ☐

How was Drug Regimen altered in response to the event?

Not altered	☐		
Altered due to AE	☐	*Specify below*	
Reduced	☐	**Date[1]**	
		New dose (units)	
Temporally interrupted	☐	**Stopped date[1]**	
		Restart date[1]	
Permanently discontinued	☐	**Date[1]**	
Rechallenge	☐	**Date[1]**	

1. *All dates must be reported as dd-MMM-yyyy*
2. *For an intermittent dosing regimen (e.g., cyclic therapy), if the event occurred between two cycles, enter the start date as the start date of first administration of the first cycle.*
3. *For a dose escalation regimen, enter the dose at the time of the event. This date is of particular importance for intermittent dosing regimens (e.g., cyclic therapy).*

2. Medical History

Hepatitis history including A, B, C, D and E	☐		Biliary non-obstructive	☐		History of alcohol abuse	☐
Autoimmune hepatitis	☐		Previous DILI *(specify suspected drugs below)*	☐		Obesity	
Recent exposure to blood products/body fluids/ transfusion	☐		Fatty liver or steatohepatitis	☐		Exposure to toxic agents	☐
Dyslipidemia	☐		Heart failure	☐		Recent travel to countries with endemic hepatitis infections	☐
Biliary obstructive disease	☐		Other causes of hyperbilirubinemia	☐		Other relevant conditions *(specify below)*	☐
Recent Intravenous drug abuse	☐		Diabetes *(specify if uncontrolled below)*	☐		Other relevant risk factors *(specify below)*	☐
Malignancy	☐		Haemodynamic shock	☐		Unknown	☐

If any item is checked above, please describe relevant details, i.e., onset date, signs and symptoms, laboratory values, duration, diagnostic tests, treatment and outcomes.

3. Concomitant Medications

Please provide relevant concomitant medications (including prescription medications, OTC drugs, herbal and dietary supplements). Please ensure consistency with data reported on the standard SAE reporting form.

Product	Suspected	Total daily dose/Units	Start Date[1,2]	Ongoing	Last dose date[1,3] prior to AE
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	
	☐			☐	

1. ***All dates must be reported as dd-MMM-yyyy***
2. ***For an intermittent dosing regimen (e.g., cyclic therapy), if the event occurred between two cycles, enter the start date as the start date of first administration of the first cycle.***
3. ***For a dose escalation regimen, enter the dose at the time of the event. This date is of particular importance for intermittent dosing regimens (e.g., cyclic therapy).***

4. Clinical Signs and Symptoms

Signs and Symptoms	Yes	Onset date[1]	Ongoing	Resolution date[1]
Nausea	☐		☐	
Vomiting	☐		☐	
Malaise	☐		☐	
Reduced appetite	☐		☐	
Fatigue	☐		☐	
Dark urine	☐		☐	
Light colored feces	☐		☐	
Abdominal pain	☐		☐	
Jaundice	☐		☐	
Pruritis	☐		☐	
Hepatomegaly	☐		☐	
Splenomegaly	☐		☐	
Encephalopathy	☐		☐	

Signs and Symptoms	Yes	Onset date[1]	Ongoing	Resolution date[1]
Hepatic dysfunction	☐		☐	
Ascites	☐		☐	
Esophageal varices	☐		☐	
Rash	☐		☐	
Fever	☐		☐	
Eosinophilia	☐		☐	
Other organ involvement *(specify below)*	☐		☐	
Other *(specify below)*	☐		☐	
1. All dates must be reported as dd-MMM-yyyy				

5. Liver Biochemical Tests

	ALT		AST		GGT		ALP		Total Bilirubin		Direct Bilirubin		PT/INR	
	Value	xULN	Value	xULN	Value	xULN	Value	xULN	Value	xULN	Value	xULN	Value	xULN
Reference Range														
Units														
Baseline														
Date														
Date														
Date														
Date														
Date														
Date														
Date														
Date														
Date														
Date														
Date														
Date														
All dates must be reported as dd-MMM-yyyy														

6. Virology Tests:

Please specify if not done (ND) in the results section

Type of Test	Date[1]	Results
Hepatitis A- IgM		
Hepatitis A- IgG		

Type of Test	Date[1]	Results
Hepatitis B		
HBsAg		
Anti- HBs		
Anti-HBc IgM		
HBeAg		
Anti-HBe		
HBV DNA		
Hepatitis C		
Anti-HCV		
HCVRNA		
Hepatitis D		
Hepatitis E		
EBV IgM		
EBV IgG		
CMV IgM		
CMB IgG		
Others infections *(specify below)*		
1. All dates must be reported as dd-MMM-yyyy		

7. Autoantibodies for Immunologic Studies

Please specify if not done (ND) in the results section

Type of Test	Date[1]	Results
Antimitochondrial antibody (AMA)		
Antinuclear antibody (ANA)		
Anti-smooth-muscle antibody (ASMA)		
Antineutrophil cytoplasmic antibody (ANCA)		
Anti-liver/kidney microsomal antibody (anti-LKM)		

Others *(specify below)*		
1. All dates must be reported as dd-MMM-yyyy		

8. Hepatic Imaging and Liver Biopsy

Please specify if not done (ND) in the results section

Type of Test	Date[1]	Results
Ultrasound		
CT scan		
Magnetic resonance imaging (MRI)		
Magnetic resonance cholangiopancreatography (MRCP)		
Endoscopic retrograde cholangiopancreatography (ERCP)		
Hepatobiliary iminodiacetic acid (HIDA)		

Type of Test	Date[1]	Results
scan		
Liver biopsy		
Others *(specify below)*		
1. All dates must be reported as dd-MMM-yyyy		

9. Treatment/Procedures for DILI

Treatment[1]/Procedure	Total daily dose/Units	Start Date[2,3]	Ongoing	Last dose date[2,4] prior to AE
			☐	
			☐	
			☐	
			☐	
			☐	
			☐	
			☐	
			☐	
			☐	
			☐	
			☐	
			☐	
			☐	
			☐	
			☐	

Treatment[1]/Procedure	Total daily dose/Units	Start Date[2,3]	Ongoing	Last dose date[2,4] prior to AE
			☐	
			☐	
			☐	

1. ***E.g., glucocorticoid, ursodeoxycholic acid***
2. ***All dates must be reported as dd-MMM-yyyy***
3. ***For an intermittent dosing regimen (e.g., cyclic therapy), if the event occurred between two cycles, enter the start date as the start date of first administration of the first cycle.***
4. ***For a dose escalation regimen, enter the dose at the time of the event. This date is of particular importance for intermittent dosing regimens (e.g., cyclic therapy).***

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: .....

ANNEX 5

PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

ANNEX 5

PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

Not Applicable

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

Safety checklist for:

- Photosensitivity Reaction and Rash
- Clinically Relevant Drug-Induced Liver Injury (DILI)

MOCK-UP OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (DETAILS OF SAFETY CHECKLIST)

SAFETY CHECKLIST FOR PRESCRIBING PHYSICIAN

Esbriet (pirfenidone)

Before initiating Esbriet (pirfenidone), and in addition to reading the Summary of Product Characteristics, please check each of the following:

Drug-induced Liver Injury

Prior to initiation of treatment:

- ☐ The patient does not have severe hepatic impairment or end stage liver disease. Esbriet is contraindicated in patients with severe hepatic impairment or end stage liver disease
- ☐ Liver function tests have been performed prior to initiation of treatment with Esbriet
- ☐ I am aware that elevations of serum transaminases can occur during treatment with Esbriet
- ☐ The patient is informed that serious liver injury may occur and that he/she should contact their prescribing physician or regular physician immediately for clinical evaluation and liver function tests if symptoms of liver injury including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice (as described in the patient information leaflet) occur.

During treatment:

- ☐ Liver function tests will be performed monthly in the first six months of treatment
- ☐ Liver function tests will be performed every three months thereafter during treatment
- ☐ Patients who develop liver enzyme elevations will be closely monitored and the dose of Esbriet will be adjusted or treatment will be permanently discontinued if necessary (please refer to the Summary of Product Characteristics for recommendations)
- ☐ Prompt clinical evaluation and liver function tests will be performed if a patient develops symptoms or signs of liver injury (please refer to the Summary of Product Characteristics for recommendations).

Photosensitivity

- ☐ The patient is informed that Esbriet is known to be associated with photosensitivity reactions and that preventive measures have to be taken
- ☐ The patient is advised to avoid or reduce exposure to direct sunlight (including sunlamps).

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- The patient is instructed to use a sunblock daily, to wear clothing that protects against sun exposure, and to avoid other medications known to cause photosensitivity.
- The patient is informed that he/she should report to the prescribing physician or regular physician if any new and significant skin rash occurs.

Reporting of adverse events

Healthcare professionals should report any adverse events suspected to be associated with the use of Esbriet according to national reporting requirements.

If you are aware of any suspected adverse reactions associated with the use of Esbriet, including clinically significant photosensitivity reactions and skin rashes, drug-induced liver injury, clinically significant abnormal liver function tests and any other clinically significant ADRs, please report such information to <<<<AFFILIATE ADDRESS and CONTACT DETAILS>>>>>>.

[Date month/year]

<<<Roche Affiliate name and

Full contact detail>>>

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ANNEX 7

OTHER SUPPORTING DATA

(INCLUDING REFERENCED MATERIAL)

ANNEX 7

OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

American Thoracic Society/European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. Am J Respir Crit Care Med 2000;161:646–64.

Hyldgaard C, Møller J, Bendstrup E. Changes in management of idiopathic pulmonary fibrosis: impact on disease severity and mortality. Eur Clin Respir J 2020;7:1807682.

King TE Jr, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008;177:75–81.

King TE Jr, Brown KK, Raghu G, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;184:92–9.

King TE Jr, Tooze JA, Schwarz MI, et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001;164:1171–81.

Kondoh Y, Taniguchi H, Kataoka K, et al. Disease severity staging system for idiopathic pulmonary fibrosis in Japan. Respirology 2017;22:1609–14.

Ley B, Bradford WZ, Vittinghoff E, et al. Predictors of mortality poorly predict common measures of disease progression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2016;194:711–8.

Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012;156:684–91.

Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011;377:1760–9.

Raghu G, Anstrom KJ, King TE Jr, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366:1968–77.

Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788–824.

Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018;198:e44–68.

Raghu G, Wells AU, Nicholson AG, et al. Effect of nintedanib in subgroups of idiopathic pulmonary fibrosis by diagnostic criteria. Am J Respir Crit Care Med 2017;195:78–85.

Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011;365:1079–7.

Yamauchi H, Bando M, Baba T, et al. Clinical course and changes in high-resolution computed tomography findings in patients with idiopathic pulmonary fibrosis without honeycombing. PLoS One 2016;11:e0166168.

Post-Authorization Use in Populations Not Studied in Clinical Trials

Pregnant and Breastfeeding Women

Idiopathic pulmonary fibrosis (IPF) is a disease of the elderly, and two-thirds of patients with IPF are older than 60 years at the time of presentation (American Thoracic Society/European Respiratory Society 2000).

Therefore, pregnancy is a rare occurrence in the IPF population and no reliable data are available concerning the use of pirfenidone in pregnant women. Nevertheless, in animals, placental transfer of pirfenidone and/or its metabolites occurs with the potential for accumulation of pirfenidone and/or its metabolites in amniotic fluid. At high doses (≥ 1000 mg/kg/day), rats exhibited prolongation of gestation and reduction in fetal viability. As a precautionary measure, it is thus, preferable to avoid the use of pirfenidone during pregnancy.

It is unknown whether pirfenidone or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of pirfenidone and/or its metabolites in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk (E.U. Summary of Product Characteristics, see Section 5.3). Therefore, a risk to the breastfed infant cannot be excluded.

ANNEX 8

SUMMARY OF CHANGES TO THE RISK-MANAGEMENT PLAN OVER TIME

ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval Date [a] Procedure	Change
01	15 December 2010 (RMP in place at time of authorization)	**Identified risks** 1. Photosensitivity reaction and rash 2. Abnormal liver function tests, increased ALT and AST levels 3. Dizziness 4. Weight loss 5. Gastrointestinal symptoms 6. Fatigue **Potential risks** 1. Falls 2. Specific cardiac events [b] 3. Increased platelet count 4. Off-label use 5. Potential drug interactions (including smoking) **Missing information** 1. Patients being treated concomitantly with immunosuppressants 2. Patients with secondary causes of pulmonary fibrosis 3. Patients with preexisting risk factors for hepatic dysfunction such as alcohol abuse and diabetes 4. Patients with preexisting prolonged QT interval 5. Patients with severe underlying cardiac, hepatic or any other form of pulmonary disease 6. Patients treated concomitantly with other IPF treatments 7. Patients suffering from severe stages of IPF 8. Exposure during pregnancy and lactation
02	14 February 2012	• Blood dyscrasias were added as a potential risk

Version	Approval Date [a] Procedure	Change
03	11 October 2012	• The potential risk of Drug interactions (including smoking) was updated to Potential drug interactions (including smoking, ciprofloxacin and warfarin) • Results from FUM drug-drug interaction PK Study PIPF-017 (ciprofloxacin) were included
04	29 April 2013	• Addition of severe skin reactions as a potential risk • Requested following PRAC review of PSUR03 which included 1 serious case of toxic skin reaction
05	10 January 2014	• Added information regarding post-marketing experience with increased AST and ALT in combination with increased total serum bilirubin • Added information regarding agranulocytosis as a post-marketed event • Requested following PRAC review of PSUR04 • Requested following CHMP review of safety variation submitted October 2013
06	01 May 2014	• Added event of angioedema as important identified risk • Updated cumulative and period post-marketing data from the PSUR 6 period
07	27 Oct 2014	• Added information from Study PIPF-016 (ASCEND). No new safety concerns were added. • Updated cumulative and period post-marketing data from the PSUR 7 period
7.1	15 April 2015	• Information added to comply with PRAC PSUR 7 request to revise RMP sections • Updated document to include details of Roche acquisition of InterMune
7.2	27 July 2015	• No changes made to safety concerns • Per feedback from PRAC (EMEA/H/C/PSUSA/00002435/201502), minor errors were corrected in the table of risk minimisation measures (Part V, Section 3 and Part VI, Section 1.4)

Version	Approval Date [a] Procedure	Change
8.0	21 March 2016	• No changes made to the list of safety concerns • The primary purpose of this E.U. RMP update was to support the Esbriet film-coated tablet extension application • Sections reflecting details of the capsule formulation were updated to include details of the tablet formulation based on the updated SmPC • Relevant details from the Phase I bioequivalence Study GP29830 were included • Contents of the E.U. RMP were transferred from the InterMune template to the Roche template that is aligned with the EMA specified format (July 2013) and sections were updated to reflect current information, where appropriate • Annexes were updated, as appropriate, to reflect latest information • In addition, several editorial changes were made for clarity
8.1	28 September 2016	Added the following important potential risk as requested by CHMP: • Risk of Medication Error in Patients Transferring between Capsules and Tablets • Clarified in “Product Overview” that the capsule will remain on the market once the tablet is marketed • The Important Potential Risk of Medication Error in Patients Transferring between Capsules and Tablets was incorporated in all relevant sections of the E.U. RMP Routine updates from PBRER 9 (post-marketing exposure, off-label use, medication error; effectiveness of additional risk minimization measures) were included in the modular sections of the E.U. RMP.
8.2	23 February 2017 EMEA/H/C/002154/X/0035/G	• Table VI.2.4 (Risk of Medication Error in Patients Transferring Between Capsules and Tablets) was updated with text proposed by the PRAC • Deleted the important potential risk of “Increased Platelet Count” throughout the document per the CHMP recommendation in the final assessment report for Esbriet PBRER 9 (Procedure number EMEA/H/C/PSUSA/00002435/201602) • Annex 11 (Mock-Up of Proposed Additional Risk Minimization Measures): Changed “Capsules” to “Esbriet” in a single instance, and version number was added

Version	Approval Date [a] Procedure	Change
9.0	07 May 2018 EMEA/H/C/002154/IB/0051	• Transition of RMP contents to the revised GVP Module V 9R2) template – Reclassification of all safety concerns in alignment with the GVP Module V (R2) regulation • Status of the PASS (Study WB29908/PIPF-025/PASSPORT) was updated from ongoing to completed. Based on results from this study and related PRAC feedback (EMEA/H/C/PSR/S/0011), the following changes are summarized in this RMP version: Removal of missing information for the following relevant sub-populations: – Advanced stages of IPF (baseline FVC < 50%) – Concomitant immunosuppressive therapies – Concomitant other therapies for IPF – Predisposing conditions for liver disease – Secondary causes of pulmonary fibrosis – Underlying hepatic disease – Underlying other forms of pulmonary disease
10.0	EMEA/H/C/002154/II/0066/G	• Version 10.0 of the Esbriet E.U. RMP is updated to align with the updated E.U. SmPC that further characterizes the risk of liver toxicity associated with Esbriet (pirfenidone). Additionally, the post-marketing exposure was updated based on the most recent Esbriet PBRER (PBRER 1092142; DLP 27 February 2019), and the Epidemiology section was updated based on the updates from the most recent Esbriet Investigator's Brochure (Version 14). • The Safety Checklist in Annex 6 was updated to include information on DILI. The DHPC and DIL were also added to Annex 6. • A guided questionnaire for DILI was added to Annex 4.

Version	Approval Date [a] Procedure	Change
10.1	EMEA/H/C/002154/II/0066/G	Version 10.1 of the Esbriet E.U. RMP is updated to address the comments raised in the PRAC Rapporteur assessment report: • The identified risk “Clinically relevant DILI” was re-termed “DILI” and the risk characterization of DILI and other relevant parts of the RMP were updated accordingly • Guided questionnaire for DILI (Annex 4), safety checklist and DHPC letter for DILI (Annex 6) revised • Pharmacovigilance plan for the important potential risk of “severe skin reactions” amended to reflect completion of Study WB29908/PIPF-025 • Summary of the RMP amended to align with updates and references to dossier sections and scientific literature deleted • Post-marketing exposure updated based on the most recent Esbriet PBRER (PBRER 1100405, DLP 27 February 2020)
10.2	01 October 2020 EMEA/H/C/002154/II/0066/G	Version 10.2 of the Esbriet E.U. RMP is updated to address the comments raised in the PRAC Rapporteur assessment report: • “Missing information” safety concerns noted in Part II, Section 4 have been summarized in Part VI, Summary Section II.B. The summary was removed in error in E.U. RMP Version 9.0. • Updated to align with the requested changes to the E.U. SmPC Section 4.4 in which hepatic function and DILI are now presented separately, with DILI described under a dedicated sub-heading

Version	Approval Date [a] Procedure	Change
11.0	EMEA/H/C/002154/II/0069 This application was withdrawn on 19 May 2021; therefore, E.U. RMP v11.0 was never approved. The list of changes that were proposed in v11.0 is retained for awareness.	• New indication of UILD was added in Part II: Module SI-Epidemiology of the Indication and target population • Product Overview Table was updated to include all necessary updates on the new indication of UILD • Clinical trial exposure data was added for the new indication of UILD in Part II: Module SIII • Part II: Module SIV.1 was updated with Exclusion Criteria in pivotal clinical studies within the development program (Study MA39189) for the indication of UILD • Part II: Module SIV.3 was updated with Limitations in Respect to Populations typically underrepresented in Clinical Trial Development Program for the indication of UILD • Post-authorization exposure data was updated for the indication of IPF • Part II: Module SVII.3 was updated with information on UILD for important identified risks, potential risks, and missing information • Part V Risk Minimization Measures was updated to include indication of UILD • Updated Guided Questionnaire for DILI was added to Annex 4 of the RMP • Removal of DHPC and DIL for Clinically Relevant DILI from Annex 6 of the RMP
12.0	EMEA/H/C/002154/II/0074	• Amend existing authorized IPF indication to remove the restriction limiting treatment to adult patients with mild to moderate IPF • Product Overview Table was updated to align with the updates to the E.U. SmPC • Part II: Module SI was updated to include disease classification and was aligned with the GVP Guidance: Population-Specific Considerations III: Pregnant and Breastfeeding Women • Part II: Module SIII – Clinical Trial Exposure was updated to include exposure-adjusted analyses of pooled clinical trials in IPF • Part II: Module SIV.1 – Exclusion criteria in pivotal clinical studies within the development program was updated with additional criteria • Part II: Module SV – Post-authorization experience was updated as per the most recent PBRER (1106411) with the DLP of 28 February 2021 • Part II: Module SVII.2 – New Safety Concerns and Reclassification with a Submission of an Updated RMP was updated with rational for removing severe skin reactions, previously classified as an important potential risk, from the list of safety concerns

Version	Approval Date [a] Procedure	Change
		• The important potential risk of severe skin reactions was removed from Part II: Module SVIII – Summary of the Safety Concerns and Part II: Module SVII 3.3 Information on Important Potential Risks • Severe skin reactions safety concern was removed from V.1 Routine Risk Minimization Measures and V.3 Summary of Risk Minimization Measures • PASS Category was added for the completed Study WB29908 in Annex 2 • Updated Guided Questionnaire for DILI was added to Annex 4 of the RMP • DHPC and DIL for Clinically Relevant DILI were removed from Part V.2 Additional Risk Minimization Measure and Annex 6 of the RMP • Pregnant and Breastfeeding Women information was added in Annex 7 to align with the GVP Guidance: Population-Specific Considerations III: Pregnant and Breastfeeding Women
12.1	EMEA/H/C/002154/II/0074	**Part II, Module SII** • Gastrointestinal symptoms cross-reference removed from the discussion of gastrointestinal symptoms section in safety pharmacology **Part II, Module SV, SV.1.1** • Added Patient Year: Total Pills / (7.2 pills × Persistence × 365 days) as a method used to calculate exposure per PBRER RDR 1113548, DLP 27 February 2022 **Part II, Module SV, SV.1.2** • Exposure in Tables 12 and 13 updated in line with PBRER RDR 1113548, DLP 27 February 2022 **Part II, Module SVII, SVII.2** • Rationale for removal of the safety concerns in the updated RMP, in line with the Assessment Report for procedure number EMEA/H/C/002154/II/0074

Version	Approval Date [a] Procedure	Change
		Part II, Module SVII, SVII.3.1 • The following safety concerns have been removed: – Gastrointestinal symptoms – Risk of medication error in patients transferring between capsules and tablets – Patients with QT prolongation – Patients with underlying specific cardiac events **Part II, Module SVII, SVII.3.2** • Prolongation of QT and underlying specific cardiac events were removed as missing information per procedure EMEA/H/C/002154/II/0074. **Part II, Module SVIII** • The following safety concerns have been removed from the summary of safety concerns: – Gastrointestinal symptoms – Risk of medication error in patients transferring between capsules and tablets – Patients with QT prolongation – Patients with underlying specific cardiac events **Part III.1** • Gastrointestinal symptoms were removed as safety concern for which other forms of routine PV activities are in place Overall, none of these concerns are subject to additional pharmacovigilance activities and no additional risk minimization measures are in place. The SmPC describes the routine risk minimization measures in place for Gastrointestinal symptoms, and these symptoms are well-recognized and well-characterized. Following continued post-marketing monitoring by the MAH, no safety signal has emerged for the other safety concerns. Therefore, it is considered that at this stage of the product life cycle these safety concerns can be removed from the RMP. **Part V** • Reference to the relevant sections of the Patient Information Leaflet have been added to the risk minimization measures

Version	Approval Date [a] Procedure	Change
		• The following safety concerns have been removed from routine risk minimization measures: – Gastrointestinal symptoms – Risk of medication error in patients transferring between capsules and tablets **Part VI** Specific references to parts of the CTD and studies have been removed

CHMP = Committee for Medicinal Products for Human Use; CTD = common technical document; DHCP = Dear Healthcare Professional; DIL = Dear Investigator Letter; DILI = drug-induced liver injury; DLP = data lock point; EMA = European Medicines Agency; FUM = ferrous fumarate; FVC = forced vital capacity; GVP = Good Pharmacovigilance Practices; IPF = idiopathic pulmonary fibrosis; PASS = post-authorization safety study; PBRER = Periodic Benefit-Risk Evaluation Report; PK = pharmacokinetic; PRAC = Pharmacovigilance Risk Assessment Committee; RMP = Risk Management Plan; SmPC = Summary of Product Characteristics; UILD = unclassifiable interstitial lung disease.

[a] Refers to the date of CHMP positive opinion. Note, not all versions of the E.U. RMP are approved by the CHMP.

[b] Supraventricular tachyarrhythmia, atrioventricular block/sick sinus syndrome, ventricular arrhythmia, bundle branch block, aortic or pulmonic valvular incompetence.