Australian Public Assessment Report for pirfenidone

Proprietary Product Name: Esbriet

Sponsor: Roche Products Pty Ltd

August 2016

TGA | Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.

- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.

- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.

- AusPARs are prepared and published by the TGA.

- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.

- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.

- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated Partial Thromboplastin Time
ASA	Australian-Specific Annex
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Curve
$AUC_{0-24\,h}$	Area Under the Curve (0 to 24 hours)
AUC_{0-72h}	Area Under the Curve (0 to 72 hours)
BCS	Biopharmaceutics Classification System (FDA)
CDS	Core Data Sheet
CER	Clinical Evaluation Data
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum plasma concentration post dose
CNS	Central Nervous System
CYP	Cytochromes P450
ddY	Deutschland, Denken et Yoken mouse
DL_{CO}	Diffusing capacity of the lung for arbon monoxide
DHCPL	Dear healthcare professional letter
ECG	Electrocardiogram
ED_{50}	Half maximal effective dose
FBS	Fetal Bovine Serum

Abbreviation	Meaning
FDA	Food and Drug Administration (USA)
GD	Gestation Day
GI	Gastrointestinal system
HDPE	High Density Polyethylene
hERG	human Ether-à-go-go-Related Gene
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IFN-γ	Interferon gamma
IL-12	Interleukin-12
Ki	Binding affinity
LD_{50}	Median Lethal Dose
LD_{50}	Median Lethal Dose
LFT(s)	Liver Function Test(s)
LPS	Lipopolysaccharide
MMP	Metalloproteinase
MRHD	Maximum Recommended Human Dose
NAC	N-acetyl-cysteine
NCE	New Chemical Entity
NMT	Not More Than
PCS	Pharmaceutical Sub-Committee
PDE	Permitted Daily Exposure
PDGF	Platelet Derived Growth Factor
PDGF	Platelet Derived Growth Factor
P-gp	P-glycoprotein
PI	Product Information
PO	Oral administration (*latin: per os*)

Abbreviation	Meaning
PK	Pharmacokinetic
PD	Pharmacodynamic
PSUR	Post-marketing Safety Update Reports
RE	Relative Exposure
RMP	Risk Management Plan
SAE	Serious adverse event
SAS	Special Access Scheme
SD	Sprague Dawley
SPC	Summary of Product Characteristics
TDS	Three Times Daily
TE	Treatment emergent
TEAEs	Treatment emergent adverse event
TGF-β1	Transforming Growth Factor beta1
T_{max}	Time to peak plasma concentration
TNFα	Tumour Necrosis Factor alpha
ULN	Upper Limit of Normal
UV	Ultraviolet
VEGF	Vascular Endothelial Growth Factor
w/w	Weight for weight
WHOCC	World Health Organisation Collaborating Centres

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	5 February 2016
Date of entry onto ARTG:	29 February 2016
Active ingredient:	Pirfenidone
Product name:	Esbriet
Sponsor's name and address:	Roche Products Pty Ltd PO Box 255 Dee Why NSW 2099
Dose form:	Hard capsules
Strength:	267 mg
Container:	HDPE bottle
Pack size:	270 tablets
Approved therapeutic use:	*Esbriet is indicated for the treatment of idiopathic pulmonary fibrosis (IPF)*
Route(s) of administration:	Oral
Dosage:	Treatment dose: Three 267 mg tables (801 mg per dose) taken three times daily (total daily dose = 2,403 mg) following 14 day dose escalation period. See approved Product Information (PI) for full details of dosage and administration
ARTG number:	235577

Product background

This AusPAR describes the application by Roche Products Pty Ltd (the sponsor) to register capsules containing 267 mg of the new chemical entity (NCE) pirfenidone under the trade name Esbriet. The application was for the indication of:

> *'the treatment of idiopathic pulmonary fibrosis (IPF)'*

Pirfenidone is the first drug in its pharmacological class and has been placed in the WHOCC (World Health Organisation Collaborating Centres) ATC (Anatomical Therapeutic Chemical Classification) drug class of other immunosuppressants' and has been designated an ATC drug code of L04AX05.

The exact mechanism of action has not yet been fully established. It is and described as an anti-fibrotic agent with anti-inflammatory properties.

Idiopathic pulmonary fibrosis (IPF) is a distinct form of irreversible chronic fibrosing interstitial pneumonia of unknown aetiology. It generally occurs in older adults, is limited to the lungs and is associated with a histological/radiological appearance known as 'usual interstitial pneumonia'. It is a rare condition with a prevalence estimated at between 2 and 29 cases per 100,000 of the population. The clinical course is characterised by debilitating loss of lung function resulting in respiratory insufficiency, with an estimated median survival after diagnosis of 2.5 to 5 years. Early medical treatments for IPF were largely ineffective, and despite being a rare condition, currently IPF accounts for approximately 23% of lung transplantations performed worldwide, usually for selected younger patients.

One view of pathogenesis of IPF postulates fibroblastic foci and excess collagen following release of pro-fibrotic mediators such as platelet derived growth factor (PDGF) and possibly vascular endothelial growth factor (VEGF) due to micro-injuries to alveolar epithelium. The aetiology of initial alveolar cell injury is as yet unknown.

In 2011 the American Thoracic Society and other international respiratory organisations published Evidence-based Guidelines for Diagnosis and Management for IPF.[1]

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 29 February 2015.

Australian regulatory status

Pirfenidone has not previously been submitted to the TGA for approval within Australia. Through the Special Access Scheme (SAS) of Australia, pirfenidone has been occasionally prescribed usually through the requests of respiratory specialists to supply on a named patient basis or to specified patients who were participants in clinical trials. Pirfenidone does not have orphan drug status.

International regulatory status and approval history

Pirfenidone was first approved for the treatment of IPF in Japan in 2008.

Pirfenidone has since been approved for the indication of '*mild to moderate idiopathic pulmonary fibrosis*' in the EU (February 2011) and Canada (October 2012), and for the treatment of idiopathic pulmonary fibrosis in the US (October 2014) and Switzerland (September 2015)

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

---

[1] Raghu G 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.

II. Quality findings

Introduction

The sponsor proposed to register hard opaque capsules containing 267 mg pirfenidone. The active ingredient is a new chemical entity with the structure shown below (Figure 1). It has an unclear mechanism of action, and has been placed in the 'other immunosuppressant' class by the WHOCC.

The recommended effective and maximum dose is 2,403 mg/day (three 267 mg capsules taken three times daily (TDS), therefore a maximum of nine capsules/day).

Drug substance (active ingredient)

Figure 1: Structure of pirfenidone and basic properties of the active drug substance
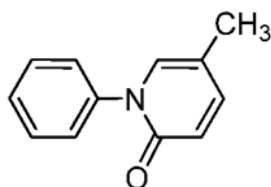
Pirfenidone
(5-methyl-1-phenyl-2-1(H)-pyridone)
Molecular formula: $C_{12}H_{11}NO$
Molecular weight: 185.22
CAS No.: 53179-13-8
pK_a: -0.2 ± 0.6
Laboratory code: PIRF, PIR, S-7701, AMR 69, PP191

The drug substance pirfenidone is an achiral, non-hygroscopic white to pale yellow powder. Pirfenidone has been shown to have high permeability. The solubility and permeability profiles suggest that pirfenidone is a Biopharmaceutics Classification System (BCS) Class 1 drug.[2]

There is only one polymorphic form of pirfenidone, designated as Form A, which was identified during the phase transition studies. The polymorphic form was not affected by the milling process and the manufacturing processes of the drug product. Form A of pirfenidone was used in all non-clinical and clinical studies.

The quality control of the drug substance (including the drug substance specification) is mostly acceptable. The proposed specification limits have been adequately justified except for the limit for one of the specified impurities. Although the proposed limits for specified and unspecified impurities comply with the International Conference on Harmonisation (ICH) identification/qualification threshold (0.05%), this limit was not accepted by the toxicological Delegate for specified impurity D of the pirfenidone monograph in the European Pharmacopoeia.[3]

Drug product

The following table lists each ingredient, with respective quantities (in mg) and function of each excipient in the drug product:

---

[2] BCS (of the FDA, USA) Class 1 drug refers to any drug with high permeability and high solubility under certain laboratory criteria.

[3] Reference to specified impurity in this AusPAR refers to detectable impurity D of the pirfenidone monograph (European Pharmacopoeia: 01/2016:2856). Impurity limits were accepted and the issue was resolved at the time of approval. For further discussion on acceptance of impurity limits, please refer to the Section VI: Overall conclusion and risk/benefit assessment.

Table 1: Drug product excipients

Exipients	
Capsule fill	Pirfenidone
	Croscarmellose sodium
	Cellulose (microcrystalline)
	Povidone
	Magnesium stearate
	Purified water
Capsule shell	Hard gelatin capsule #1
	Opacode Brown

q.s. (quantum statis) = the amount needed for drug product manufacture

The product is an immediate release oral capsule containing 267 mg of pirfenidone and four other conventional pharmaceutical excipients including croscarmellose sodium, microcrystalline cellulose, povidone and magnesium stearate. The hard gelatin capsule of size #1 is a small capsule size, which was chosen to facilitate capsule administration in patients who are generally older and with difficulty in swallowing.

Two formulations were used in the pivotal clinical studies; 133 mg and 267 mg capsules. The 267 mg capsules used in the clinical studies consist of the same formulation as the proposed commercial formulation with exception of the source of the capsule shell (bovine/porcine origin) and the ink printing design (the proposed 'PFD267 mg' versus 'Intermune 267 mg' in clinical trials). These differences were acceptable.

The quality of the product is controlled by acceptable specification that includes tests and limits for appearance, identification, assay, dose uniformity, impurities, water content, and dissolution of the drug substance. Microbiological quality is also controlled by microbial limits. The assay release and expiry specification limits comply with the TGA's Therapeutic Goods Order No. 78 (TGO 78) and the impurities limits comply with the ICH guidance and are acceptable.[4] The analytical methods used to analyse the product were adequately described and validated.

The stability data supplied supported a shelf life of 48 months for the unopened product when it is stored below 30°C. Once opened, the product may be stored for a maximum period of 2 months, with storage below 30°C

Biopharmaceutics

No absolute bioavailability study was performed by the sponsor. Justification for not providing the absolute bioavailability study was on the basis that pirfenidone is a highly soluble and highly permeable drug substance with pharmacokinetic properties suggestive of high oral bioavailability. Given the rapid in vitro dissolution (> 80% in 10 minutes), the company believes that the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time.

---

[4] Therapeutic Goods Order No. 78, Standard for Tablets and Capsules (29/10/2008) applying to Part 3-1 of the Therapeutic Goods Act 1989.

A food effect study (Study PIPF-005) was provided in this submission. The study comprised of a single dose and a multi dose bioavailability study. Assessment was based on the single dose study only, in which the pharmacokinetics of orally administered pirfenidone capsules under fasted and fed conditions, and when administered with and without antacids were examined. The outcomes of the study are summarised below:

- The single-dose study demonstrated that the metabolite 5-carboxy-pirfenidone (5-CA-pirfenidone) was the only significant first pass metabolite. However, this major metabolite does not appear to be biologically active, based on evidence to date.

- The presence of food significantly reduced the rate and extent of absorption of pirfenidone. The PI states (under Absorption):

  - 'Administration of Esbriet with food results in a large reduction in C_{max} (by 50%) and a smaller effect on AUC (area under the curve), compared to the fasted state. Following oral administration of a single dose of 801 mg to healthy older adult volunteers (50 to 66 years of age) in the fed state, the rate of pirfenidone absorption slowed, while the AUC in the fed state was approximately 80 to 85% of the AUC observed in the fasted state.'

  - The half-lives of absorption were longer under fed conditions. However, given the reduction in adverse experience reported under fed condition, the company has proposed to include a recommendation that the product is to be given with food on the PI.

- Administration of antacid did not affect the rate or extent of absorption of the drug substance.

- Although the multi-dose study was not evaluated by the Pharmaceutical Chemistry Sub-Committee, it was noted that the study indicated that both pirfenidone and the 5-CA-pirfenidone metabolite showed decreased clearance with increasing dose given. Oral clearance is saturable with increasing dose, particularly at above 2,403 mg/day, which has been set as the maximum recommended daily dose.

These results were brought to the attention of the Clinical Delegate so that they could consider:

- Whether it is acceptable from a clinical perspective for the product to be given with or without food.

- Whether the proposed maximum recommended daily dose (based on the results from this multi-dose bioavailability study) is acceptable.

Quality summary and conclusions

Approval is not recommended with respect to chemistry and quality control because there are unresolved issues as summarised below:

- The proposed limit of NMT 0.05% for the specified impurity in the drug substance has not been qualified

- No data has been provided to demonstrate that the qualified limit of NMT 0.0055% for specified impurity in the drug substance can be met.

The company has been informed of ways to address these issues.

There were biopharmaceutical issues that were brought to the attention of the Clinical Delegate for consideration on the basis of the biopharmaceutical Study PIPF-005; specifically whether it is acceptable from a clinical perspective for the product to be given

with food and whether the results from the multi-dose bioavailability study (Study PIPF-005) support the proposed maximum recommended daily dose of 2,403 mg/day.

III. Nonclinical findings

Pharmacology

Primary pharmacology

IPF is a form of chronic fibrosing interstitial pneumonia that is restricted to the lung with unknown aetiology. The pathogenesis of IPF involves inflammation and fibrosis. The sponsor has proposed that pirfenidone has both anti-inflammatory and anti-fibrotic properties, but a clear mechanism of action has not been identified. The in vitro and in vivo studies submitted support some anti-inflammatory and anti-fibrotic effects of the drug.

Anti-inflammatory effects

Pirfenidone inhibited the release of tumour necrosis factor alpha (TNFα) in response to lipopolysaccharide (LPS) in a human monocyte cell line with an half maximal inhibitory concentration (IC_{50}) value of 48 μg/mL. This is approximately 3 times the clinical maximum serum concentration (C_{max}) for total pirfenidone (14.7 μg/mL or 79 μM), suggesting these effects may not be clinically relevant. Pirfenidone metabolites were not seen to have clinically relevant anti-inflammatory activity in this assay due to either very low clinical exposure (5-OH-pirfenidone) or only very weak inhibitory activity (5-CA-pirfenidone). Pirfenidone did not have anti-oxidant properties or inhibit cyclooxygenase activity in vitro.

In vivo studies examined the anti-inflammatory activity of pirfenidone in a variety of animal models. In mice sensitised with D-galactosamine, 500 mg/kg of oral (PO) pirfenidone attenuated LPS induced mortality and reduced hepatocyte necrosis and apoptosis. Consistent with this, pirfenidone attenuated the release of the pro-inflammatory cytokines (TNFα, interleukin 12 (IL-12) and interferon gamma (IFNγ)) as well as the pro-fibrotic cytokine transforming growth factor beta 1 (TGF-β1), and increased levels of the anti-inflammatory cytokine IL-10 at doses approximating the maximum recommended human dose (MRHD) on a body surface area basis. The half maximal effective dose (ED_{50}) for inhibition of TNFα release was 148 mg/kg/day, which is approximately one third the MRHD based on mg/m². Similarly, pirfenidone reduced inflammation induced swelling in a variety of rat models, with effects reported at doses as low as 10 mg/kg PO. However, these study reports lacked detail, and used relatively crude methods of measuring oedema, limiting confidence in the interpretation of these studies. Unlike its parent, the 5-CA-pirfenidone metabolite (≤ 500 mg/kg PO) produced no significant inhibition of LPS induced TNFα production in mice.

Anti-fibrotic effects

Pirfenidone weakly inhibited the proliferation of a human lung fibroblast cell line in vitro. In unstimulated lung fibroblasts, inhibition was not dose dependent, with small reductions in proliferation observed at 100 and 1,000 μM. Pirfenidone (1,000 μM) inhibited proliferation by approximately 50% in lung fibroblasts stimulated with platelet derived growth factor (PDGF), but not interleukin 1beta (IL-1β). In contrast, nintedanib (approved by the TGA for IPF in September 2015) inhibited lung fibroblast proliferation in response to PDGF with an EC50 of 0.01 μM. Furthermore, pirfenidone did not inhibit collagen

production in lung fibroblasts in response to TGF-β1 at concentrations up to 1,000 μM. Pirfenidone appeared to have greater anti-fibrotic activity in a human dermal fibroblast cell line. Pirfenidone (≥ 30 μM) inhibited proliferation in unstimulated dermal fibroblasts in the absence of fetal bovine serum (FBS). However, inhibition of proliferation in the presence of FBS and in response to TGF-β1 or IL-1β was observed only at 1,000 μM pirfenidone. Collagen production in response to TGF-β1 stimulation was inhibited by pirfenidone (≥ 300 μM). Collagenase release was promoted by pirfenidone in unstimulated, but not IL-1β-stimulated dermal fibroblasts. In a human monocyte cell line, pirfenidone attenuated the release of TGF-β1 in response to LPS, but these effects were less pronounced in the presence of FBS. A secondary pharmacology screening assay found the inhibition of the following matrix metalloproteinases (MMP): MMP-3, MMP-8, MMP-12 and MMP-13. However, based on the IC_{50} values (0.7 to 1.5 mM), it is unlikely that inhibition of MMP would occur clinically.

The anti-fibrotic effects of pirfenidone were also assessed in rodent models of bleomycin induced lung fibrosis. Prophylactic administration of pirfenidone markedly reduced fibrotic lesions, with associated reductions in bleomycin-induced lung hydroxyproline content and prolyl hydroxylase activity in hamsters (0.5% w/w in diet, approximately 500 mg/kg/day[5]; relative exposure (RE) 1.6 x based on mg/m² body surface area doses). Inflammatory markers were also reduced by pirfenidone (malondialdehyde content, myeloperoxidase and superoxide dismutase activity). Similarly, prophylactic treatment attenuated fibrosis development in rats (≥ 300 mg/kg/day PO (diet), RE 1.1 x based on mg/m²) and mice at subclinical exposures (based on AUC).[6] However, treatment with pirfenidone had little effect on established fibrosis in rats. There was a trend towards decreased fibrosis score after 4 weeks treatment with 30 to 300 mg/kg/day pirfenidone, but there was no effect on lung hydroxyproline content. In mice, pirfenidone appeared to arrest the development of bleomycin induced lung fibrosis (at 30 and 100 mg/kg/day PO TDS; RE, 0.04 to 0.08 x based on AUC). An anti-fibrotic mechanism of pirfenidone was also supported by a published study in dogs with induced chronic heart failure.[7]

Together, the primary pharmacology data provide some evidence to support an anti-inflammatory and anti-fibrotic mechanism of action. The in vitro studies did not identify the pharmacological target or provide compelling evidence for clinically relevant mechanisms of action. However, the in vivo data did provide evidence of the ability of pirfenidone to modulate inflammatory and fibrotic pathways in response to pathological stimuli. This included inhibition of fibrosis progression at clinically relevant doses (based on comparison of doses adjusted for body surface area, or plasma AUC).

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamic studies revealed that pirfenidone inhibited radio ligand binding to a number of human transporters, receptors and/or enzymes at high concentrations and with relatively low affinity. The highest affinity interaction was at rolipram binding sites in rat brain (binding affinity (Ki): 222 μM; IC_{50}, 621 μM). As the clinical C_{max} was approximately 79 μM at the MRHD, it is unlikely that any clinically significant interaction with the screened targets would occur.

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular, respiratory and gastrointestinal (GI) systems. CNS studies in ddY mice[8] revealed dose dependent sedation and ptosis (≥ 30 mg/kg PO), with hypothermia,

---

[5] Based on a 100 g hamster eating 10 g of food per day

[6] Oku H et al. Antifibrotic action of pirfenidone and prednisolone: Different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. *Eur. J. Pharmacol.* 2008; 590: 400–408.

[7] Lee KW et al. Pirfenidone prevents the development of a vulnerable substrate for atrial fibrillation in a canine model of heart failure. *Circulation.* 2006; 114: 1703–1712.

[8] ddY mouse = Deutschland, Denken and Yoken mouse, strain commonly used in medical research

hypoactivity and abnormal posture observed after a single dose of ≥ 100 mg/kg (estimated RE < 0.1 x and 0.2 x based on mg/m² doses, respectively). In addition, doses of 300 mg/kg were associated with staggering gait and abnormal limb position (estimated RE 0.6 x based on mg/m²). These adverse neurological signs resolved by 2 h post-dose. In a preliminary study, 1,000 mg/kg PO pirfenidone was associated with similar CNS effects as well as convulsions, rearing behaviour, palpebral opening and respiratory inhibition, with mortality in 3 of 4 mice occurring within 10 minutes of dosing (estimated RE 1.9 x based on mg/m²). Pirfenidone increased pentobarbital induced sleep time and displayed analgesic activity in the acetic acid induced writhing test in mice (≥ 100 mg/kg, significant at 300 mg/kg). Pirfenidone (300 mg/kg) also increased the threshold for electroshock and pentylenetetrazole induced convulsions in mice. The sponsor proposed that some of the observed CNS effects may be related to the binding and/or inhibition of centrally expressed receptors and transporters demonstrated in radio ligand studies. This is considered plausible as C_{max} values were approximately 1 or 2 mM in B6C3F1 mice that received a single oral dose of 500 or 1,000 mg/kg pirfenidone, respectively, and transfer across the blood brain barrier was high.[9] However, these effects are not expected clinically given the C_{max} value of 0.08 mM at the MRHD.

In vitro, pirfenidone dose dependently inhibited hERG potassium ion channel current with an IC_{50} of approximately 5 mM, which is around 60 x the clinical C_{max} for total pirfenidone and approximately 150 x the peak plasma concentration of unbound drug. The major metabolite, 5-CA-pirfenidone, did not inhibit hERG channels at concentrations up to 1 mM (20 x C_{max}). In addition, pirfenidone and 5-CA-pirfenidone did not prolong action potential duration in guinea pig papillary muscles at concentrations up to 1 mM.

In rats, pirfenidone decreased blood pressure and increased heart rate, arterial blood flow and the incidence and frequency of premature ventricular contractions (≥ 30 mg/kg intra-duodenal (ID) administration). Atrioventricular block was also observed in addition to premature ventricular contractions in conscious rats that received ≥ 100 mg/kg. There were no treatment related ventricular abnormalities in dogs. In anaesthetised dogs, pirfenidone increased heart rate and markedly reduced blood pressure at doses of ≥ 100 mg/kg ID, which was associated with a C_{max} around 7 x that expected clinically. Pirfenidone also increased heart rate in conscious dogs within 2 h of dosing with ≥ 30 mg/kg PO or IV, with sinus tachycardia also observed following PO/IV dosing (approximately 100 mg/kg, 4 x clinical C_{max}). In conscious dogs, pirfenidone did not significantly decrease blood pressure at doses up to 300 mg/kg PO. QT prolongation was observed in one study at a dose of 100 mg/kg PO in dogs. However, pirfenidone did not prolong QT interval in the high dose group of the same study (300 mg/kg), or in a subsequent study that involved administration at 100 mg/kg PO or 97 mg/kg IV. With the exception of decreased RR and PR intervals associated with increased heart rate, there were no treatment related electrocardiogram (ECG) effects of pirfenidone at doses up to 300 mg/kg (around 14 x clinical C_{max}, based on Study NCR251). In both rats and dogs, the effects of pirfenidone on blood pressure appeared greater in anaesthetised compared to conscious animals. In anaesthetised dogs, continuous IV infusion led to severe lowering of blood pressure and respiratory suppression after infusion of approximately 150 to 200 mg/kg, with death occurring after infusion of around 450 mg/kg.

Respiratory studies in rats and dogs gave mixed results. Respiratory volume was increased up to 1.5 fold in anaesthetised rats that received ≥ 30 mg/kg pirfenidone ID. An increase in respiratory rate was observed in conscious dogs dosed at 300 mg/kg PO, but this appeared to be secondary to emesis and increases in activity and heart rate. A subsequent study in conscious dogs found no adverse effects of pirfenidone on respiratory rate, tidal volume or minute volume (≤ 100 mg/kg PO or IV; RE, 4 x C_{max}). Mild acidosis

---

[9] Based on C_{max} values of 173/217 and 367/385 µg/mL in male/female mice that received 500 or 1,000 mg/kg pirfenidone in Study NCR001

was observed in conscious dogs following IV dosing with pirfenidone (around 30 mg/kg and over; RE, 2 x C_{max}), but was generally reversed by 4 h post-dose.

In vitro, pirfenidone modestly decreased muscle tone in isolated rabbit ileum (100 µM). In vivo, pirfenidone dose dependently inhibited the rate of gastric emptying (> 40%) and small intestinal transit (> 20%) in fasted rats at doses of ≥ 30 mg/kg (estimated exposure ratio of 0.5 based on C_{max}).[10] These data indicate inhibition of gastric emptying and reduced rate of intestinal transit are likely to occur clinically.

Pirfenidone (500 mg/kg/day PO) had no suppressive effects on humoral or cellular mediated immunity in a 4 day study in mice.

Pharmacokinetics

Pirfenidone was rapidly absorbed in mice, rats and dogs following oral administration, with the time taken to reach maximum plasma concentration (T_{max}) value generally < 1 h, which was comparable to humans (1.5 h). Bioavailability was moderate to high in rats, dogs and humans. Exposure increased in proportion to dose and was higher in fasted compared to fed animals. In rats, exposure decreased with repeated dosing at high dose levels which is consistent with hepatic enzyme induction. The plasma half-life was moderate in rats (approximately 2 to 3 h) and short in dogs and humans (< 2 h and approximately 2 h, respectively).

Plasma protein binding was saturable in all species and was low in mouse and rat plasma (approximately 30%) and moderate (approximately 55%) in dog and human plasma. The volume of distribution was similar to total body water in dogs and humans indicating modest tissue distribution. In rats, oral administration of ^{14}C-pirfenidone resulted in widespread and fairly rapid distribution of radioactivity; highest levels were observed in the kidney, nasal cavity, liver and preputial gland, with retention of radioactivity in the latter. Peak levels in the lung (target organ) were comparable to the plasma C_{max} (1.2 x). Distribution to the brain and testis was 0.9 x and 0.4 x the peak level in plasma respectively.

Pirfenidone was metabolised by hydroxylation and subsequent carboxylation leading to the formation of 5-CA-pirfenidone, which was the major metabolite in all species. Low levels of the intermediate metabolite, 5-hydroxy-pirfenidone were observed in plasma in rats and humans. There were no other plasma metabolites. Three minor metabolites were observed in the urine, bile or faeces of rats, dogs and/or humans. In humans and dogs, the dominant circulating species was pirfenidone; with 5-CA-pirfenidone present at 70 to 80% the level of the parent drug. 5-CA-pirfenidone was the dominant circulating species in mice and F344 rats, with metabolite to parent ratios of 1 to 2 in Sprague Dawley (SD) rats. Multiple cytochrome P450 enzymes (CYPs) were found to be capable of catalysing the formation of 5-CA-pirfenidone, with CYP1A2 identified as the predominant enzyme responsible. CYPs 2C9, 2C19, 2D6 and 2E1 also contribute to pirfenidone metabolism.

Pirfenidone was predominantly excreted via the urine (80 to 90%), almost exclusively as 5-CA-pirfenidone in all species. In animals, faecal excretion accounted for < 10% of the dose. Enterohepatic recirculation was also demonstrated in animals.

Together, these data demonstrate a high degree of similarity in the pharmacokinetic profile of pirfenidone in rats, dogs and humans. The ratio of 5-CA-pirfenidone to pirfenidone was markedly higher in mice and F344 rats, making SD rats and beagle dogs

---

[10] Based on a C_{max} of 7.2 µg/mL in rats that received 30 mg/kg (Study PCLN-PIRF-077)

(as used in the pivotal repeat dose toxicity studies) more suitable models for assessing the toxicity profile of pirfenidone.[11, 12]

Pharmacokinetic drug interactions

The potential for pirfenidone to interact with other drugs was not fully assessed, with no studies on the effect of pirfenidone on transporters other than P-glycoprotein (P-gp) submitted.[13] Given the high predicted intestinal concentration (1.7 mM) the lack of studies on intestinal transporters is considered a deficiency. Studies with P-gp indicated that pirfenidone was not a substrate for P-gp, but was a weak inhibitor. The estimated IC_{50} was > 1 mM, with approximately 30% inhibition at this concentration. Therefore, inhibition of P-gp may occur clinically. Delayed gastric emptying and reduced intestinal motility by pirfenidone (as observed in safety pharmacology studies) may alter the absorption of other medicines.

Pirfenidone inhibited a number of CYP isoforms in experiments conducted using human liver microsomes, but only at very high concentrations (estimated IC_{50} values > 1 mM; > 12 x C_{max}), therefore, the CYP inhibitory activity of pirfenidone is not considered to be clinically relevant.

The ability of pirfenidone to induce CYPs was partially investigated as effects on activity, but not gene expression level. Pirfenidone modestly induced (approximately 2 to 4 fold) CYP1A, 2B, 2D and/or 3A activity in B6C3F1 mice that received ≥ 800 mg/kg/day as a dietary admixture for 4 weeks (RE, 0.1 x based on AUC).[14] Stronger induction of CYP2B activity was observed following dietary administration at ≥ 375 mg/kg/day for 4 weeks in F344 rats (≥ 7 fold; RE 0.3 x),[15] and ≥ 500 mg/kg/day PO for 6 months in SD rats (≥ 4 fold; RE, 1 x based on AUC). Modest induction of CYP1A (<3 fold) and 3A4/5 (< 2.5 fold) were also observed in SD rats that received up to 1,000 mg/kg/day for 6 months. Dose dependent induction of CYP activity, including CYP2B (≤ 3 fold) and 3A (≤ 2 fold), was also observed in repeat dose studies in dogs (RE, 1 to 3 x based on AUC). In rodents and dogs, the pattern of CYP induction was similar to that induced by phenobarbital. However, in cultured human hepatocytes, pirfenidone (250 µM) showed only modest induction of CYP2C19 and 3A activity, and in one of three donors, also 1A2 or 2C9. These effects are unlikely to be relevant at the expected clinical exposure (C_{max} approximately 80 µM, with peak distribution to the liver approximately 2 x plasma C_{max}). The weight of evidence indicates that drug interactions secondary to CYP enzyme induction are unlikely during clinical use.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted by the oral route in SW and B6C3F1 mice, SD rats and beagle dogs. The maximum non-lethal doses in B6C3F1 mice and fed SD rats were 1,000 mg/kg (relative exposures of approximately 25 and approximately 13, respectively based on C_{max}).[16] The lethal dose for 50% of test animals (LD_{50}) was approximately 1,000 mg/kg in SW mice, and mortality occurred in fasted SD rats at a dose of 1,000 mg/kg

---

[11] SD rat = Sprague-Dawley rat, specific strain of rat commonly used in biomedical research
[12] F344 rat = Fischer-344 rat, specific strain of rat commonly used in biomedical research
[13] *EMA Guideline on the investigation of drug interactions* (CPMP/EWP/560/95/Rev. 1 Corr. 2**). This guideline indicates the effects of drugs on OAT, OCT and OATP transporters should be investigated, and that investigation of CYP induction should involve gene expression analysis.
[14] Based on AUC data obtained in week 4 in Study NCR018.
[15] Based on exposure ratio at 500 mg/kg/day in Study NCR014.
[16] B6C3F1 mouse = Specific hybrid strain of mouse commonly used in biomedical research.

(RE 21 to 28 x clinical C_{max}). Mortality was preceded by adverse CNS signs including hypoactivity, ataxia, salivation, ptosis, lacrimation, abnormal gait and abnormal respiration. These observations are consistent with results of safety pharmacology studies. No mortality occurred in dogs at doses up to 1,000 mg/kg/day, but weakness, emesis and hypoactivity were observed (RE of approximately 10 x clinical C_{max}). Overall, pirfenidone has a moderate to low order of acute toxicity by the oral route.

Repeat dose toxicity

Studies of up to 3 months duration were conducted in B6C3F1 mice and F344 rats, 6 months in SD rats and 9 months in beagle dogs. Dosing was by the oral route, which is the intended clinical route. In addition, two studies in SD rats involved administration of pirfenidone by continuous IV infusion for 4 weeks. Two 9 month studies were conducted in dogs using the same dose levels, but with different dosing frequency (once or twice daily), which is less frequent than the proposed clinical regimen (TDS). In rodent studies, pirfenidone was either administered once daily by gavage, or as a dietary admixture. The duration and conduct of the pivotal studies (6 months in SD rats and 9 months in beagle dogs) were consistent with the relevant international guidelines.[17] The high dose levels selected were appropriate, limited by toxicity, but not optimal due to relatively low systemic exposure. The IV studies in rats were intended to address the low relative exposure by using doses up to 2,000 mg/kg/day, but the use of continuous IV infusion introduced other confounding effects.

Relative exposure

Exposure ratios have been calculated based on animal: human plasma C_{max} and the AUC from dosing to 24 h post-dose (AUC_{0-24h} area under the curve from 0 to 24 h). Human reference values are from clinical Study PIPF-004. The C_{max} and AUC data used for animals is the mean of male and female values on the last sampling occasion. As shown in Table 2 the relative exposure after repeated dosing was low in all species. Higher exposures were achieved on the first day of dosing in rats by both the PO and IV route.

Limited toxicokinetic data were available for 5-CA-pirfenidone (the major circulating metabolite). Exposure ratios for this compound in 13 week dietary studies were ≤ 1.4 in B6C3F1 mice and ≤ 6.2 in F344 rats, despite the relatively high metabolite to parent ratios. Toxicokinetic data for 5-CA-pirfenidone were not obtained in the pivotal studies. Based on metabolism data, exposure ratios for the 5-carboxy metabolite can be assumed to be higher than for the parent in the pivotal rat study and similar to those for the parent in the pivotal dog study. Exposure ratios for the metabolite in rats treated by continuous IV infusion are lower compared with those for the parent.

Table 2: Relative exposure in repeat dose toxicity and carcinogenicity studies.

Species	Study details	Route; Sampling occasion	Dose (mg/kg/day)	C_{max} (µg/mL)	Exposure ratio based on C_{max}	$AUC_{0-24 h}$ (µg·h/mL)	Exposure ratio based on AUC
Mouse (B6C3F1)	3 months (NCR013) (dose range-finding for carcinogenicity)	PO (diet) Week 13	200	0.9	< 0.1	16	<0.1
			600	1.5	0.1	26	0.1
			2,000	3.4	0.2	47	0.3
	2 years (NCR018) (carcinogenicity)	PO (diet) Week 4	800	1.3	< 0.1	24	0.1
			2,000	2.5	0.2	41	0.2

---

[17] ICH M3(R2): Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals and Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1)

Species	Study details	Route; Sampling occasion	Dose (mg/kg/day)	C_{max} (µg/mL)	Exposure ratio based on C_{max}	$AUC_{0-24\,h}$ (µg·h/mL)	Exposure ratio based on AUC
			5,000	3.7	0.3	56	0.3
Rat (SD)	4 weeks (PCLN-PIRF-118)	IV Day 1	500	13	0.9	259	1.4
			1,000	56	3.8	820	4.6
			1,625	96	6.5	1456	8.1
	6 months (PCLN-PIRF-073) (pivotal)	PO (gavage) Week 26	20	6.1	0.4	19	0.1
			100	15	1.0	105	0.6
			500	48	3.3	183	1.0
			1,000	73	4.9	337	1.9
Rat (F344)	3 months (NCR014) (dose range-finding for carcinogenicity)	PO (diet) Week 13	500	4.8	0.3	70	0.4
			1,000	9.3	0.6	153	0.9
			1,500	10.9	0.7	188	1.0
	2 years (NCR017) (carcinogenicity)	PO (diet)*	375	3.6	0.2	53	0.3
			750	7.1	0.5	112	0.7
			1,500	10.9	0.7	188	1.0
Dog (Beagle)	9 months (PCLN-PIRF-072) (pivotal)	PO (capsule) Week 39	20	22	1.5	47	0.3
			70	76	5.1	181	1.0
			200	166	11	570	3.2
Human (patients)	steady state (Study PIPF-004)	PO; steady state	(2,403 mg)	14.7	–	180	–

= animal: human plasma AUC_{0-24h}; * = based on 13-week data obtained in Study NCR014.

Major toxicities

The major target organs for pirfenidone were the liver, kidney, urinary bladder, submaxillary gland and the haematopoietic and CNS systems. Some effects were also observed in thyroid, adrenal glands, prostate, uterus and lymphoid tissues. Adverse gastrointestinal symptoms including emesis occurred in high dose groups, but generally only at the initiation of dosing.

In liver, hepatocellular hypertrophy, generally in the centrilobular zone, was consistently observed in all species at low (≤ 3 x) or subclinical relative exposures (based on AUC). Increased liver weight and induction of hepatic enzyme activity, in particular CYP1A, 2B, 2D and/or 3A were also observed from lower exposures. Consistent with enzyme induction[18], a 'ground glass' appearance of hepatocytes was evident in F344 rats and beagle dogs that received 1,500 or 200 mg/kg/day PO for 3 or 9 months, respectively (RE, 1 x and 3 x). Clinical chemistry changes consistent with liver changes were also seen in rats and dogs (increased alkaline phosphatase (ALP) and/or cholesterol). Other liver findings included hepatocyte necrosis in SD rats (1,000 mg/kg/day; RE, approximately 2), fatty change in F344 rats (≥ 1,000 mg/kg/day; RE, approximately 1) and perivascular inflammation in dogs (with treatment for 3 months at 200 mg/kg/day and after 9 months at ≥ 70 mg/kg/day; RE, ≥ 1 x). All of the observed changes in liver were reversible. In addition, thyroid follicular hyperplasia was observed in a male SD rat that received 1,000 mg/kg/day pirfenidone PO. This is consistent with increased thyroid hormone production secondary to increased metabolism associated with liver enzyme induction.

In F344 rats, kidney weights were dose dependently increased with tubular epithelial degeneration and regeneration observed at ≥ 1,000 mg/kg/day (RE, approximately1 x). Urinalysis was not performed in F344 rats. In SD rats, increased specific gravity and

---

[18] Maronpot RR et al. Hepatic enzyme induction: histopathology. *Toxicol. Pathol.* 2010; 38: 776–795.

decreased urine pH were observed (≥ 100 mg/kg/day; RE, 0.6 to 1.9 x); there was also a high incidence of crystalluria in females (≥ 500 mg/kg/day) and males (1,000 mg/kg/day). Histopathological changes in kidneys (pelvic cavity dilatation and slight inflammation) and urinary bladder (inflammation of lamina propria and transitional cell hyperplasia) occurred at the high dose level (1,000 mg/kg/day; RE, approximately 2 x) at low incidence and may have been secondary to crystalluria. The urinary changes may have been related to the high levels of urinary excretion of the 5-CA-pirfenidone metabolite. The observed changes were reversible in SD rats. There was no evidence of adverse kidney or urinary bladder effects in dogs (RE, ≤ 3.2 x in the pivotal study).

Haematological changes included mild anaemia in SD and F344 rats that received ≥ 1,000 mg/kg/day pirfenidone for 3 to 6 months (RE, approximately1 to 2 x). There was also a slight reduction in erythrocytes in dogs that received ≥ 70 mg/kg/day pirfenidone for 9 months (RE, ≥ 1 x). The magnitude of the changes was small and findings were reversed following cessation of dosing. Platelets were increased after 3 or more months treatment with pirfenidone in B6C3F1 mice (2,000 mg/kg/day; RE 0.3 x), F344 rats (1,000 mg/kg/day; RE 0.9 x) and beagle dogs (≥ 70 mg/kg/day; RE ≥ 1 x). The increase was shown to be reversible in dogs. There was a slight prolongation of the activated partial thromboplastin time (APTT) in rats that received ≥ 500 mg/kg/day PO or 300 mg/kg/day IV pirfenidone, which was reversible in the oral study (RE, 1 x).

Adverse neurological effects of pirfenidone were identified in safety pharmacology studies. Similar effects were observed in the rat and dog studies, which included hypoactivity, salivation, abnormal gait, hypopnea and convulsions. The clinical signs were primarily observed in the highest dose groups and most frequently occurred after the first dose of pirfenidone was administered. Splitting the high dose of 200 mg/kg/day into two 100 mg/kg doses reduced the severity of clinical signs in dogs.

Increased relative adrenal gland weight was associated with slight zona fasciculata hypertrophy in male F344 rats that received 1,500 mg/kg/day pirfenidone in the diet for 3 months (RE, 1 x). There was also a slight increase in the incidence of vacuolisation of fasciculata cells in male SD rats that received 1,000 mg/kg/day PO (RE, 1.9 x). Diffuse cortical hypertrophy/hyperplasia was also observed in premature decedent female SD rats that received 1,625 mg/kg/day pirfenidone IV (RE, approximately 8 x). The adrenal gland was not a target organ for toxicity in dogs.

Submaxillary gland changes were observed in dogs. Acinar hypertrophy of the mucous gland was seen in animals that received pirfenidone at 200 mg/kg/day for 3 months and at ≥ 70 mg/kg/day for 9 months (RE, ≥ 1 x), accompanied by increased weight of the submaxillary gland at the 200 mg/kg/day dose level (≥ 3 months treatment). These changes were considered to be related to the increased salivation in these dogs. There was evidence from both the 3 and 9 month studies to indicate these changes were reversible.

Atrophy was reported in the prostate or uterus of dogs that received 200 mg/kg/day pirfenidone PO for 3 months. These findings were not replicated in the 9 month dog studies, and their toxicological significance is unclear.

Genotoxicity

The genotoxic potential of pirfenidone was assessed in a standard battery of validated studies conducted in compliance with ICH guideline[19]. Concentrations/doses used were appropriate. Pirfenidone was not mutagenic in assays in bacteria (Ames test), and was not clastogenic in in vitro assays using Chinese hamster lung and ovary cells. In vivo, pirfenidone was tested in a micronucleus assay in ICR mice and unscheduled DNA synthesis assay in F344 rats (PO administration), with negative results returned. Together, these studies indicate that pirfenidone does not pose a genotoxic hazard.

Carcinogenicity

Two year carcinogenicity studies were conducted in which pirfenidone was administered as a dietary admixture to B6C3F1 mice (800 to 5,000 mg/kg/day) and F344 rats (375 to 1,500 mg/kg/day). In general, the design and conduct of studies was consistent with ICH guidelines S1B and S1C[20][21]. Dose selection was appropriate, with use of maximum tolerated doses demonstrated as reduced body weight gain and total body weight (by > 10%) in the mid and high dose groups. However, despite the high dose levels employed, the relative exposure margins were ≤ 1 in both species at all doses. Margins are higher with respect to exposure to the metabolite, 5-CA-pirfenidone, noting that in mice, the metabolite to parent ratio ranged from 1.6 to 14 x, and in rats the range was 2.4 to 4.5 x, while in humans, the ratio was approximately 0.6 to 0.8 x in respect of 5-CA-pirfenidone to pirfenidone.

Dose dependent hepatocellular adenomas and carcinomas were observed in mice that received ≥ 800 mg/kg/day pirfenidone (RE, 0.1 x), in male rats that received ≥ 750 mg/kg/day pirfenidone (estimated RE, 0.7 x) and in female rats that received 1,500 mg/kg/day (RE, 1 x). Treatment related hepatoblastomas were also observed in male mice that received ≥ 800 mg/kg/day pirfenidone. Associated non-neoplastic liver findings included hepatocellular hypertrophy, single cell necrosis, eosinophilic foci of cellular alteration, pigmented Kupffer cells and hepatocytes, hepatocellular steatosis and angiectasis. The neoplastic changes in rodent liver are likely related to the observed phenobarbital like induction of CYP enzymes following repeated dosing with pirfenidone. Induction of CYP activity was demonstrated in B6C3F1 mice and F344 rats that received the same doses as in the carcinogenicity study for 4 weeks. Given that induction of CYPs was not observed with pirfenidone in vitro in experiments with cultured human hepatocytes, and considering that there is some evidence that human hepatocytes are less sensitive to the hyperplastic and anti-apoptotic effects of CYP inducers compared with rodent cells,[22,] the finding of hepatocarcinogenicity in rodents may not be applicable to patients. However, the clinical relevance of the finding cannot be excluded, particularly given the occurrence of the liver tumours at subclinical exposure levels (as low as 0.1 x).

There was an apparent increase in thyroid follicular cell carcinomas in rats that received 1,500 mg/kg/day PO pirfenidone. The mechanism of action for these tumours is related to induction of liver enzymes and is considered rodent-specific due to species differences in thyroid hormone regulation.[23]

---

[19] ICH Guideline; S2 (R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use

[20] ICH Guideline; S1A: Testing for Carcinogenicity of Pharmaceuticals

[21] ICH Guideline; S1C (R2): Dose Selection for Carcinogenicity of Pharmaceuticals

[22] Holsapple MP, et al. Mode of action in relevance of rodent liver tumors to human cancer risk. *Toxicol. Sciences.* 2006; 89: 51–56

[23] Alison RH, et al. Neoplastic lesions of questionable significance to humans. *Toxicologic Pathol.* 1994; 22: 179–186

The incidence of uterine adenocarcinomas was dose dependently increased in female rats that received ≥ 375 mg/kg/day PO pirfenidone (4%, 12%, 16% and 26% in control, 375, 750 and 1,500 mg/kg/day groups, respectively; statistically significant at high dose). Cystic and/or glandular endometrial hyperplasia was also more prevalent in female rats that received ≥ 750 mg/kg/day pirfenidone. The sponsor proposed that the mechanism of action for the development of uterine tumours was related to effects of pirfenidone on hypothalamic dopamine release and subsequent suppression of prolactin levels. Mechanistic studies were conducted that showed a single oral dose of pirfenidone (≥ 100 mg/kg) increased extracellular dopamine levels in the arcuate nucleus of the hypothalamus, but not in striatum, of rat brain. However, data on plasma hormone levels were inconclusive in a study that administered 1,500 mg/kg/day pirfenidone as a dietary admixture for 4 weeks to female F344 rats. After one week, pirfenidone treated rats had modest increases in plasma oestrogen and marked suppression of progesterone and prolactin. However, the effects on oestrogen and progesterone were attenuated with time, with the oestrogen to progesterone ratio decreasing from 7.3 in Week 1 to 1.7 in Week 4. Furthermore, plasma prolactin levels at Week 4 were abnormally high in both the control and pirfenidone treated groups, preventing a conclusion on treatment related effects. The mechanistic studies provided were insufficient to demonstrate a dopamine/prolactin driven oestrogen dominance mechanism of action for the observed uterine adenocarcinomas. In addition, if oestrogen dominance were to be established, the consequence of liver enzyme induction and subsequent modulation of oestrogen metabolism should also be considered.[24] The human relevance of the observed uterine tumours is not clear as a mechanism of action has not been established. Given that tumours were observed at relative exposure levels of ≤ 1 x it is possible that these tumours may be clinically relevant.

In summary, liver, thyroid and uterine tumours were observed in rodent carcinogenicity studies at subclinical exposure levels. The thyroid tumours are unlikely to be relevant to humans based on species difference in thyroid hormone regulation. The mechanism of liver tumour development is likely to be more relevant to rodents than humans, based on species sensitivity to liver enzyme induction. The data provided to support a prolactin mediated mechanism of uterine tumour development were insufficient to demonstrate a rodent specific mechanism. The predominance of 5-CA-pirfenidone exposure in rodents creates further uncertainty about the human relevance of the observed tumours. Carcinogenic activity for pirfenidone has been clearly demonstrated in the studies, but the relevance of this to humans remains unclear.

Reproductive toxicity

Studies assessing the effects of pirfenidone on fertility, embryofetal development and pre/post-natal development were conducted in SD rats. A pilot and main embryofetal development study was also conducted in Japanese white rabbits. In rats, two studies were conducted with a combined fertility and embryofetal development design. This approach is consistent with recommendations in ICH S5 (R2)[25] for drugs in which repeated administration results in altered pharmacokinetic properties and is justified as exposure to pirfenidone in non-pregnant SD rats was reduced over time. The timing and duration of dosing and groups sizes were consistent with guideline ICH S5 (R2). In rats, the first fertility and embryofetal development study used only two dose levels administered

---

[24] Yoshida M, et al. Dietary indole-3-carbinol promotes endometrial adenocarcinoma development in rats initiated with N-ethyl-N′-nitro-N-nitrosoguanidine, with induction of cytochrome P450s in the liver and consequent modulation of estrogen metabolism. *Carcinogenesis.* 2004; 25: 2257–2264.
[25] ICH Guideline; S5 (R2): Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility.

as a dietary admixture, but the deficiencies of this study were compensated for by the second study which used gavage dosing at four dose levels.

Relative exposure

No toxicokinetic data were collected in pregnant rats. In the main study of pregnant rabbits, toxicokinetic data were restricted to measurement of plasma pirfenidone at 0.5 and 24 h post-dose on gestation day (GD) 6 and GD18. In the pilot rabbit study, toxicokinetic data were collected and relative exposures based on AUC_{0-6h} on GD18 were calculated. For the main studies, relative exposures were estimated based on body surface area adjusted doses.

Available toxicokinetic data in non-pregnant rats support the use of body surface area adjusted doses to reasonably estimate relative exposure. In SD rats, the relative exposure to pirfenidone after a single PO dose of 1,000 mg/kg/day was 15, which decreased to 2.4 following 6 months repeated dosing;[26] and in rats dosed at 100 mg/kg/day, the exposure ratio based on plasma AUC (0.4 to 0.7 x) was similar to that estimated from body surface area (0.4 x). The estimated relative exposures achieved in the rabbit reproductive toxicity studies were low, with exposure ratios based on AUC in the pilot study being 3 to 10 x lower than that estimated for body surface area. Despite the subclinical or low relative exposure, the high dose levels were associated with maternal toxicity and were therefore considered adequate.

Table 3: Relative exposure estimates in reproductive toxicity studies

Species	Study	Dose		AUC_{0-6h} (μg·h/mL)	Exposure ratio	
		mg/kg/day	mg/m²/day		BSA[#]	AUC
Rat (SD)	Fertility and embryofetal development (Study PCLN-PIRF-078)	50	300	–	0.2	
		150	900	–	0.6	
		450	2,700	–	1.7	
		1,000	6,000	–	3.8	
	Pre/post-natal development (Study PCLN-PIRF-079)	100	600	–	0.4	
		300	1,800	–	1.1	
		1,000	6,000	–	3.8	
Rabbit (JW)	Embryofetal development (pilot study; SG99144)	30	360	0.2*	0.2	0.015
		100	1,200	0.8*	0.8	0.2
		300	3,600	2.3*	2.3	0.7
		600	7,200	4.5*	4.5	1.7
	Embryofetal development (Study PCLN-PIRF-080)	30	360	–	0.2	
		100	1,200	–	0.8	
		300	3,600	–	2.3	
Human (patients)	steady state	48^	1,586	180	–	

= animal: human dose based on body surface area, calculated using mg/kg to mg/m² conversion factors of 6, 12 and 33 for rats, rabbits and humans (50 kg adult), respectively; *AUC_{0-6h} values on GD18. In the 30 and 100 mg/kg/day groups approximate AUC_{0-24h} exposure as plasma pirfenidone levels were undetected at 6 h, but are likely underestimated in the higher dose groups; ^ = based on a 50 kg human receiving the MRHD of 2,403 mg/day

Pirfenidone and/or its metabolites crossed the placental barrier after a single 100 mg/kg/day PO dose of radiolabelled drug in rats. The highest levels of radioactivity in fetal tissues were observed 0.5 h post dose, with only low levels observed after 24 h. There appeared to be modest retention of pirfenidone in the amniotic fluid. At the peak concentration, levels in fetal tissues were approximately half the maternal plasma level. Pirfenidone and/or its metabolites were also excreted into milk following a single

---

[26] Based on plasma AUC in female rats in Study PCLN-PIRF-073

100 mg/kg PO dose on LD12. The concentration in milk was similar to plasma up to 0.5 h post-dose, with levels in milk higher from 2 to 24 h post-dose.

Male fertility, including sperm count and motility, were unaffected by repeated dosing with up to 1,000 mg/kg/day PO pirfenidone in SD rats (RE, ≤ 1.9 x).[27] Irregular oestrus cycles were observed in female SD rats that received ≥ 450 mg/kg/day PO pirfenidone (RE, ≥ 1.7 x based on mg/m^2). Oestrus cycle length was more than two fold greater in females that received 1,000 mg/kg/day pirfenidone compared to controls (9.9 compared with 4.1 days). Despite these effects, the fertility index was not seen to be reduced in treated females.

Pirfenidone was not teratogenic in rats at doses up to 1,000 mg/kg/day or rabbits at doses up to 300 mg/kg/day (RE of 3.8 x and 2.3 x, respectively). Maternal toxicity characterised by reduced body weight gain, food intake and/or clinical signs (including hypoactivity and hypopnea) was observed in pregnant rats and rabbits that received ≥ 150 and ≥ 100 mg/kg/day (estimated RE, 0.6 x and 0.8 x, respectively). In rabbits, 300 mg/kg/day pirfenidone led to maternal death and abortions, with one instance of premature delivery in the 100 mg/kg/day group. Delayed ossification occurred in the offspring of rats that received ≥ 450 mg/kg/day pirfenidone (RE, 1.7 x). Additional visceral variations (dilatation of ventricles in brain and heart, dilatation of ureters and increased renal pelvic cavitation) and decreased fetal weight were observed in a pilot study in which pregnant SD rats received 450 or 900 mg/kg/day pirfenidone as a dietary admixture. These changes were not observed at the same or higher doses in the pivotal study. Administration of up to 300 mg/kg/day pirfenidone during organogenesis in rabbits did not cause any fetal variations.

Maternal toxicity was more pronounced in SD rats when dosing was initiated during pregnancy, with adverse clinical signs, reduced body weight gain and decreased food intake observed in dams that received ≥ 100 mg/kg/day (estimated RE, 0.4x). In addition, 25% of females that received 1,000 mg/kg/day pirfenidone from GD6 died between GD19 and GD23 (estimated RE, 3.8 x). At this dose level, gestation length was increased and the parturition index decreased. Furthermore, total and live litter sizes were reduced. Pup weight was similar between groups at birth but was reduced from PND11 in the offspring of females that received ≥ 300 mg/kg/day pirfenidone (estimated RE, 1.1 x); at 15 weeks of age, body weight still tended to be lower in these animals compared with controls. There was no effect of pre- and post-natal exposure to pirfenidone on the behaviour, sexual maturation or reproductive performance of the offspring.

In summary, male and female fertility indices were unaffected by pirfenidone treatment in rats, although disruption of oestrus cycling was seen. The current studies indicate that pirfenidone is not teratogenic. However, adverse effects on embryofetal and postnatal development were observed (including inhibition of ossification, decreased birth index and reduced postnatal body weight gain, and also abortion, prolonged gestation and premature delivery). These effects occurred in conjunction with maternotoxicity.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.[28] This category is appropriate based on the adverse effects described in pregnant rats and rabbits.

---

[27] Relative exposure for fertility in males was based on AUC data in repeat dose Study PCLN-PIRF-073

[28] Category B3. *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.*

Antigenicity

Pirfenidone was not antigenic in active systemic anaphylaxis and passive cutaneous anaphylaxis tests conducted in guinea pigs. However, these assays are not considered to be sensitive in assessing the antigenic properties of small molecular weight drugs. Therefore, while the data provided indicate that pirfenidone was not antigenic in guinea pigs, the potential for antigenicity cannot be excluded. However, as specialised investigation of antigenicity is not required for new chemical entities this is not considered a deficiency.

Phototoxicity

The photogenotoxicity of pirfenidone and 5-CA-pirfenidone were assessed in in vitro assays. In addition, the general phototoxicity of pirfenidone was assessed in vivo.

Pirfenidone was equivocally positive in a photomutagenicity assay in bacteria, with a trend for increased mutations in the presence of UV light. However, the increase in mutations was < 2 fold which was the threshold for a positive response. Positive results were obtained for pirfenidone in a photoclastogenicity assay, but the finding should be interpreted with caution as these assays are known to be over sensitive and may give false positive results.[29] The metabolite, 5-CA-pirfenidone, was negative in an in vitro photogenotoxicity assay in bacteria, and also in a photoclastogenicity assay.

Phototoxicity was observed in hairless mice that received 500 mg/kg/day PO pirfenidone for one month (RE, 14 x based on C_{max}). Phototoxicity consisted of moderate to severe erythema following ultra violet (UV) exposure in the first two to three weeks, but erythema was not observed in response to UV exposure after that. Reversible acanthosis and single cell necrosis were observed in the epidermis (auricle and dorsal skin) of hairless mice that received pirfenidone and were exposed to UV light. Similar results were obtained in guinea pigs, with phototoxicity (dermal irritation) evident in animals that received ≥ 40 mg/kg/day for 3 days, but not at lower doses (exposure ratio, ≥ 0.8 based on C_{max}). The severity of phototoxicity was dependent on dose and UV intensity, and decreased with increased time between pirfenidone administration and UV exposure. The application of sunscreen reduced the severity of phototoxic lesions. Repeated dosing with ≤ 160 mg/kg/day PO pirfenidone did not induce photosensitisation in guinea pigs. Together, the data indicate that phototoxicity may occur clinically.

Impurities

The proposed specifications for four impurities in the drug substance are below the ICH qualification thresholds. In silico and/or in vitro analyses indicated there was no genotoxic concern for three of the proposed impurities. One impurity is genotoxic (clastogenic) however, and it is recommended that its specified limit be tightened to reduce carcinogenic risk.

Paediatric use

Pirfenidone is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

---

[29] ICH guideline S10: Photosafety evaluation of pharmaceuticals

Nonclinical summary

- The submitted nonclinical dossier was compliant with the relevant international guidelines, and all pivotal safety studies were conducted under GLP conditions

- Anti-inflammatory and anti-fibrotic effects were proposed as the mechanism of action for pirfenidone. Pirfenidone inhibited LPS induced TNFα release both in vitro and in vivo, with the latter occurring at clinically relevant doses. The in vitro anti-fibrotic effects of pirfenidone were mixed: the majority of effects were only observed at very high concentrations and effects were more pronounced in dermal compared to lung fibroblasts. When given prophylactically, pirfenidone attenuated the development of pulmonary fibrosis in response to bleomycin at subclinical exposures in mice, and also at doses approximating the maximum recommended human dose in rats and hamsters. In mice, pirfenidone appeared to arrest fibrosis development, but was ineffective at reversing established fibrosis in rats

- The molecular target of pirfenidone responsible for its primary pharmacological activity has not been identified. Binding assays against a panel of receptors, enzymes and transporters identified no clinically relevant secondary targets

- Safety pharmacology studies examined the effects of pirfenidone on the CNS, cardiovascular, respiratory and gastrointestinal systems. Adverse CNS effects were observed in mice from subclinical doses of pirfenidone; convulsions, respiratory inhibition and mortality were seen at doses approximately 2 x the MRHD based on mg/m^2 body surface area. Inhibition of human ether-à-go-go-related gene (hERG) channels was observed at high concentrations, but there was no dose-related prolongation of QT interval in dogs at exposures at 14 x the clinical C_{max} at the MRHD. Ventricular abnormalities were observed in rats but not dogs. Reduced blood pressure and increased heart rate occurred in anaesthetised rats and dogs, but only increased heart rate was observed in conscious dogs and at higher doses (14 x C_{max}). There were no adverse respiratory effects in conscious dogs at doses yielding up to 4 x the expected C_{max}. In vitro and in vivo studies indicated that delayed gastric emptying and reduced rate of intestinal transit are likely to occur clinically

- The pharmacokinetic profile of pirfenidone was highly similar between animals and humans. Pirfenidone has moderate to high bioavailability, was rapidly absorbed and has a short plasma half-life. Plasma protein binding was low and tissue distribution was wide. Peak concentrations of ^{14}C-pirfenidone derived radioactivity in the lung and brain were comparable to that in plasma in rats. CYP1A2 was the predominant CYP isoform responsible for metabolism, involving formation of the one major metabolite, 5-CA-pirfenidone. Excretion was predominantly via the urine, almost exclusively as 5-CA-pirfenidone. The plasma ratio of 5-CA-pirfenidone to pirfenidone was 0.7 to 0.8 in humans and beagle dogs. In contrast, 5-CA-pirfenidone was generally the predominant circulating species in B6C3F1 mice and SD and F344 rats, with metabolite to parent ratios of 2: 14 in mice and 1: 5 in rats. 5-CA-pirfenidone had no or negligible pharmacological activity

- Inhibition of P-gp by pirfenidone was demonstrated in vitro, and inhibition of P gp may occur clinically given the high predicted intestinal concentration. The drug is not a substrate for P gp. Inhibition of other intestinal transporters was not investigated. Clinically relevant inhibition of CYP enzymes was not observed in experiments with human liver microsomes. Pirfenidone showed phenobarbital like induction of CYPs 1A, 2B, 2D and 3A at clinically relevant exposures in vivo in animals. However, in vitro in cultured human hepatocytes, there was only weak induction of CYP1A, 2C9, 2C19 and/or 3A at concentrations > 3 x C_{max} at the MRHD. Therefore, significant induction of CYP enzymes by pirfenidone is not anticipated in patients

- Single dose toxicity studies in mice, rats and dogs indicated a relatively low order of acute toxicity for pirfenidone by the oral route

- Repeat dose toxicity studies were conducted in mice (3 months, PO), rats (up to 6 months, PO and IV) and dogs (up to 9 months, PO). The major target organs for toxicity were liver (hepatocellular hypertrophy associated with enzyme induction; all species), thyroid (hyperplasia; rats only), kidneys (pelvic dilatation and inflammation; rats only), urinary bladder (inflammation and/or hyperplasia; rats only), adrenal glands (hypertrophy; rats only) and submaxillary glands (hypertrophy; dogs only). These toxicities were observed at low or subclinical exposures (RE ≤ 3 x based on AUC), but were reversible. Mild anaemia, increased platelets, and adverse clinical CNS and gastrointestinal signs were also observed

- Pirfenidone was negative in genotoxicity assays. Long-term carcinogenicity studies were conducted in B6C3F1 mice and F344 rats. Pirfenidone was administered as a dietary admixture, which was associated with subclinical pirfenidone exposures (AUC) despite high daily doses. Pirfenidone induced hepato-carcinogenesis in both mice and rats, as well as thyroid tumours in rats. These appeared to be secondary to liver enzyme induction. Treatment related uterine tumours also occurred in rats. The sponsor proposed a rodent specific prolactin mediated mechanism for uterine tumour development, but the mechanistic data provided were insufficient to conclusively support this hypothesis

- Male fertility was unaffected by pirfenidone in rats (tested up to approximately 2 x AUC). In females, pirfenidone did not significantly affect fertility indices despite inducing irregular or prolonged oestrus cycles at low relative exposures. Pirfenidone and/or its metabolites crossed the placental barrier and were excreted in the milk of lactating rats. Pirfenidone was not teratogenic in rats or rabbits (tested up to low estimated relative exposures; 2 to 4 x based on mg/m^2 body surface area). However, abortion, maternal death, prolonged gestation, reduced pup numbers and viability were observed at estimated relative doses of less than 4 x the MRHD (mg/m^2). In addition, while pup weight was similar at birth, postnatal body weight gain was reduced in the offspring of rats that received clinically relevant doses of pirfenidone during gestation and lactation. There were no other effects of pre- and post-natal exposure to pirfenidone on behaviour, sexual maturation or reproductive performance of the offspring

- Pirfenidone was phototoxic in hairless mice and Hartley guinea pigs. Pirfenidone potentiated the development of erythema in response to UV exposure at subclinical exposures (C_{max}). The severity of phototoxicity decreased with time after pirfenidone administration, and could be attenuated by the application of sunscreen. In vitro studies of the photomutagenicity of pirfenidone appeared negative. Pirfenidone did not induce photosensitivity in guinea pigs.

Nonclinical conclusions

- The submission was of high quality overall, and contained no critical deficiencies

- While the mechanism of action has not been fully established, the primary pharmacology data indicate anti-inflammatory and anti-fibrotic activity. Pirfenidone attenuated and/or arrested fibrosis development in an animal model of pulmonary fibrosis, but did not reverse established fibrosis

- Pirfenidone caused adverse CNS effects which may be related to inhibition of centrally expressed transporters or receptors. Adverse gastrointestinal effects may be secondary to delayed gastric emptying and decreased intestinal motility

- The potential for intestinal drug-drug interactions was not fully explored. Inhibition of P-gp is predicted. The effects of pirfenidone on gastric emptying and intestinal motility may cause drug interactions clinically

- The main target organ identified in toxicity studies was the liver, with hepatocellular hypertrophy observed in all species. This appeared to be secondary to CYP induction, which was less evident in human hepatocytes. Changes in other target organs were generally of minimal severity, were reversible and were often only observed in one species

- Pirfenidone was not genotoxic, but was carcinogenic in mice and rats. Liver tumours occurred in both species at subclinical exposures, with thyroid tumours also occurring in rats. These tumours are likely to be secondary to chronic liver enzyme induction, but the clinical relevance of liver tumours cannot be ruled out due to the low exposure ratios. Uterine tumours also developed in rats and their significance to humans is unclear

- Pirfenidone was not teratogenic in rats or rabbits, but induced abortions and reduced parturition index and pup viability in rats at relatively low exposures. The proposed Pregnancy Category (B3) adequately reflects these adverse findings

- Phototoxicity was evident at subclinical doses and is likely to be clinically relevant. Nonclinical data indicated the use of sunscreens could attenuate the severity of reactions

- [Information redacted] a specified impurity in the drug substance, is genotoxic (clastogenic) and considered to pose a carcinogenic risk above that normally considered acceptable for human pharmaceuticals. It is recommended that the limit for this impurity be reduced to as low as reasonably practicable so as not to expose patients to unnecessary risk.

Comments on the Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for pirfenidone detailed in the sponsor's draft Risk Management Plan Section SII are in general concordance with those of the Nonclinical evaluator. However the following errors or inconsistencies were noted that should be addressed:

- Body weight gain was inhibited in the 13 weeks studies in rats and mice, but the RMP states there were no effects on body weight gain.

- There was an increased incidence of hepatocellular carcinoma in the rat carcinogenicity study, but the RMP states only an increase in adenoma.

- The comments regarding P-gp should be updated to reflect the available nonclinical data.

- The statement regarding the impurities having no genotoxic potential is not fully supported as specified impurity is clastogenic. This should be corrected.

Nonclinical evaluator's recommendations

- Based on the nonclinical data provided and evaluated, there were no nonclinical objections to the registration of pirfenidone for the proposed indication, subject to outstanding issues relating to the specified impurity. The carcinogenic risk posed by this impurity may be acceptable to the Delegate in the context of the proposed therapy, but should be minimised as far as reasonably practicable.

- The nonclinical evaluator made recommendations regarding the draft PI beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

IPF is a distinct form of irreversible chronic fibrosing interstitial It is a rare condition with a prevalence estimated at between 2 and 29 cases per 100,000 of the population. The clinical course is characterised by debilitating loss of lung function resulting in respiratory insufficiency, with an estimated median survival after diagnosis of 2.5 to 5 years.

Few medical treatments exist, and despite being a rare condition, currently IPF accounts for approximately 23% of lung transplantations performed worldwide, usually for selected younger patients.

NAC (used as monotherapy without azathioprine) is available for some IPF patients in Australia through the Special Access Scheme (SAS). Besides the experimental use of NAC, nintedanib is approved for treatment of IPF by the Food and Drug Administration (FDA) of the United States, and was recently approved by the TGA (August 2015).

Pirfenidone has been proposed for treatment of IPF for many years and has been an approved drug for the treatment of IPF in other countries as early as 2008.[30] The clinical development program for the product proposed for registration included 1336 healthy subjects and patients with IPF or pulmonary fibrosis, including 1098 patients assigned to receive pirfenidone at doses of 2,403 mg/day or higher. Due to its availability in other markets, post-marketing experience for pirfenidone is based on cumulative exposure of over 15,000 patient-years.

Pirfenidone has been an approved drug for the treatment of IPF in other countries such as Japan since 2008. Pirfenidone has been available on a named-patient basis on the SAS.

Guidance

There is no specific EMA guidance for the investigation of drugs for IPF. The FDA gave advice on the design of the additional Study PIPF-016.

Contents of the clinical dossier

The submission included the following clinical information:

- 6 clinical pharmacology studies, including 5 that provided pharmacokinetic data and a pharmacodynamics study on ECG effects:
  - 1 population pharmacokinetic analysis
  - 3 pivotal efficacy/safety studies: (PIPF-004, PIPF-006 and PIPF-016)
  - 2 ongoing long-term safety studies
- Pooled analyses, Post-Marketing Safety Update Reports (PSUR), Integrated Summary of Efficacy, and Integrated Summary of Safety.

---

[30] Raghu G et al. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. *Am J Respir Crit Care Med* 1999; 159: 1061–1069

In addition the sponsor also provided:

- Clinical summaries of efficacy, safety and other clinical literature
- EMA and Canadian regulatory reports

Evaluator's comments on clinical data

Overall the development program was comprehensively documented and the dossier well presented, although links to some data were not functional. The clinical evaluation was based on the submitted information from the sponsor. Other agency reports were also viewed for additional information.

Paediatric data

The submission did not include paediatric data as IPF occurs only in the adult population.

Good clinical practice

The study reports for the each study submitted addressed the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice and in accordance with any other applicable regulatory requirements.

Pharmacokinetics

Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies were provided. Table 4 shows the studies relating to each pharmacokinetic topic.

Table 4: Summary of studies providing pharmacokinetic (PK) data

PK topic	Subtopic	Study ID
PK in healthy adults	General PK (Single-dose, QT)*	PIPF 007
	General PK (Multi-dose)*	PIPF 005
	Bioequivalence† (Single dose)	Not applicable
	Bioequivalence† (Multi-dose)	Not applicable
	Food effect	PIPF 005
PK in special populations	Target population§ (Single and multiple dose)	PIPF 004
	Hepatic impairment*	PIPF 011
	Renal impairment*	PIPF 009
	Neonates/infants/children/adolescents	Not applicable
	Elderly	See Pop PK

PK topic	Subtopic	Study ID
Genetic/gender-related PK	Males versus females	See pop PK
PK interactions	CYPA12 inhibitor Fluvoxamine	PIPF 010
	Ciprofloxacin*	PIPF 017
	Smoking*	PIPF 010
Population PK analyses	Healthy subjects	PIPF-ORD1
	Target population	PIPF-ORD1, PIPF-ORD2
	Other-combined	PIPF-ORD1

*Indicates the primary aim of the study. †Bioequivalence of different formulations. §Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

The information is derived from conventional pharmacokinetic (PK) studies and population PK analyses used to fit models in compartmental analyses, using data from Phase I studies and Phase III Study PIPF-004 (PIPF-ORD1). Non-compartmental analyses provided confirmatory results.

Evaluator's conclusions on pharmacokinetics

Oral absorption, dose proportionality and aspects of metabolism of pirfenidone have been characterised sufficiently to make recommendations with respect to administration with food, dose titration, hepatic impairment and interaction with other medicines. Pirfenidone is cleared rapidly and is not expected to accumulate appreciably with multiple dosing at the proposed dosage in patients with normal hepatic and renal function.

Pharmacodynamics

Studies providing pharmacodynamic data

Information was derived from animal models and in vitro studies:

- Study PIPF-005 examined dose escalation, where a range of doses were tested in the multiple dose cohorts and the presence of food reduced the rate and extent of absorption of pirfenidone.

- Study PIPF-008 examined escalating doses in healthy young adults.

- Study PIPF-007 examined the effects on ECG effects of oral pirfenidone at clinical and supra-therapeutic doses compared to placebo or placebo with moxifloxacin in healthy volunteers.

- Study PIPF-004 had PK/pharmacodynamic (PD) exploratory analyses of data from 88 subjects who had PK exposure estimates. However, there were lower adverse event (AE) rates and differing rates of lung function decline compared with the full study population, so the subset of patients in the PK/PD analysis do not appear to be representative of the overall population in PIPF-004.

Evaluator's conclusions on pharmacodynamics

PK/PD correlation was demonstrated for common adverse effects including GI and dermatologic AEs.

Dosage selection for the pivotal studies

The PK data from Study PIPF-005 showed reduced incidence of AEs at a dose of 801 mg/day (as 267 mg capsules TDS) when taken with food. The maximum tolerated dose in Study PIPF-008 (2,403 mg/day) confirmed that at doses above 2,403 mg/day, women were likely to have significant adverse effects mainly of GI and CNS in nature resulting in discontinuation.

However the CSR for PIPF-004 stated that the maximum tolerated dose was not determined in these studies and that selection of doses and frequency of administration was based on a published Phase II study in IPF patients that used a maximum dose of pirfenidone 600 mg TDS and empirical experience generated by investigators in the USA since 1995.[31]

Doses of 1,197 mg/day and 2,403 mg/day were chosen for Study PIPF-004 and 2,403 mg/day for Study PIPF-006 and Study PIPF-016. The 2,403 mg dose was considered to be that needed to achieve efficacy based on previous clinical experience, and the 1,197 mg dose was included for additional qualitative safety and efficacy information.

Efficacy

Studies providing efficacy data

There were three Phase III randomised, double-blind, placebo-controlled, efficacy studies using the pirfenidone at the proposed dose in patients with IPF. These were:

- Study PIPF-004
- Study PIPF-006
- Study PIPF-016.

Evaluator's conclusions on efficacy

Study PIPF-004 demonstrated statistically significant difference from placebo favouring pirfenidone in change from Baseline in % predicted FVC, but in Study PIPF-006 no significant difference was shown.

Small adjustments in the inclusion criteria 'to increase the chances of disease progression' were made for Study PIPF-016. The study was larger, with changes in the definition for disease progression and clinically relevant secondary endpoints as well as the change in the presentation of the primary efficacy variable. PIPF-016 demonstrated a statistically significant difference in change from Baseline percent predicted FVC decline ≥ 10% or death, favouring pirfenidone 2,403 mg/day over placebo.

As supportive evidence, in the pooled analysis the proportion of patients with FVC decline > 10% or death was significantly reduced over 1 year; pirfenidone 14.8% versus placebo 26.3%. Analyses for all-cause mortality were also supportive.

---

[31] Azuma A, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005; 171: 1040–1047.

For regulatory purposes in the context of current international approval, efficacy of pirfenidone was satisfactorily demonstrated in a patient population with a clear diagnosis of idiopathic pulmonary fibrosis. However at Round 1 it was not clear whether this population included an appreciable number of patients with 'severe' disease or whether the indication should be restricted to 'mild to moderate' IPF, as for the EMA and Canadian approvals.

Safety

Studies providing safety data

The following studies provided safety data:

- Pivotal studies:
  - Study PIPF-004
  - Study PIPF-006
  - Study PIPF-016;
- Studies PIPF-002 and PIPF-012 (cut-off 7/8/2013);
- 7 Phase I studies.

An Integrated Safety Summary submitted to the FDA as the 2014 Resubmission Safety Update ('2014 RSU') was a review of pooled safety data, focussed on analyses of safety data for pirfenidone 2,403 mg/day versus placebo. It is the source of the information summarised in this section except where results from individual studies are mentioned.

Evaluator's Comment: The 2014 RSU referred to data sourced from the original 2009 ISS but the links were not active. These aspects could not be verified by the evaluator but are accepted as evaluated in the CHMP report.

Pivotal efficacy and safety studies

In the pivotal studies, safety data were collected as specified in study protocols:

- General AEs were recorded at every patient contact. Treatment emergent AEs (TEAEs) were defined as AEs that occurred after the first dose and within 28 days of the last dose of study treatment. AEs were classified as serious or non-serious, and graded as mild, moderate, severe or life-threatening (Grades 1 to 4)
- AEs of particular interest, including dermatologic AEs, were recorded at patient contacts
- Standard laboratory tests for haematology and chemistry. Liver chemistry tests were performed at pre-specified intervals according to the study protocol
- ECGs, physical examination, weight and vital signs.

Other studies

Study PIPF-012: As this was an extension study, 'TEAEs' were defined as pre-existing AEs that worsened after the first dose in PIPF-012, or started after first dose in PIPF-012 until 28 days after last dose.

Table 5 (below) summaries the studies and collates numbers of participants in pirfenidone or placebo arms of studies used in pirfenidone clinical development.

Table 5: Summary of studies in pirfenidone IPF clinical development program

Study Number	Phase	Study Objective	Subject Status/ Patient Diagnosis	Number of Participants		Total Unique Patients/ Subjects
				Pirfenidone	Placebo/ Control	
InterMune-Sponsored Studies: Patients with IPF/PF in Phase 2 and 3 Studies						
PIPF-002	2	Safety and efficacy	IPF/PF	83	0	
PIPF-004	3	Safety and efficacy	IPF	261	174	
PIPF-006	3	Safety and efficacy	IPF	171	173	
PIPF-012	3	Safety and efficacy	IPF	274[a]	0	
PIPF-016	3	Safety and efficacy	IPF	278	277	
Total InterMune Phase 2 and 3 IPF/PF Patients:				1067	624	1417[b]
InterMune-Sponsored Studies: Subjects in Phase 1 Studies						
PIPF-005	1	Safety, PK	Healthy	41	0	
PIPF-007	1	Thorough QTc, PK	Healthy	81	81	
PIPF-008	1	Safety, MTD	Healthy	16	4	
PIPF-009	1	Safety, PK	Healthy or renal impairment	26	0	
PIPF-010	1	Safety, DDI, PK	Healthy	54	0	
PIPF-011	1	Safety, PK	Healthy or hepatic impairment	24	0	
PIPF-017	1	Safety, DDI, PK	Healthy	27	0	
Total InterMune Phase 1 Subjects:				269	85	354
Total InterMune Phase 2 and 3 IPF/PF Patients and Phase 1 Subjects:				1336	709	1771[b]
Marnac-Initiated Studies: Patients with IPF/PF in Phase 2 Studies						
PIPF-001	2	Safety and efficacy	IPF/PF	26	26	
PIPF-003	2	Safety and efficacy	IPF/PF	27	25	
Total Marnac Phase 2 IPF/PF Patients:				53	51	104
Grand Total Unique Phase 1–3 Participants:				1382[c]	760	1865[b,c,d]

[a] PIPF-012 treated 603 patients who enrolled from the Phase 3 Studies PIPF-004 and PIPF-006; 274 had received placebo and 329 had received pirfenidone in PIPF-004 or PIPF-006; thus, 274 of 603 patients received pirfenidone for the first time in PIPF-012.

[b] The 274 patients who received placebo in PIPF-004 or PIPF-006 and pirfenidone in PIPF-012 are included only once in this total.

[c] Seven patients who received pirfenidone in PIPF-001 and later entered PIPF-002 are counted only once in this total.

[d] Three patients who received placebo in PIPF-001 and pirfenidone in PIPF-002 are included only once in this total.

DDI = drug-drug interaction, IPF = idiopathic pulmonary fibrosis, MTD = maximum tolerated dose, PF = pulmonary fibrosis, PK = pharmacokinetics, QTc = corrected QT interval.

Patient exposure

The Phase II Studies PIPF-001 (prednisolone control) and PIPF-003 (placebo control) were both terminated early. No data were located in the 2014 RISE but the sponsor included a brief summary.

Subjects contributing to pooled safety data from Phase II and III clinical studies had exposure as shown in Table 6.

Table 6. Pooled safety data (patient exposure) from Phase II and Phase III clinical studies

Study Number (Indication)	Total Number of Patients	Mean Duration of Treatment (Range)
Phase 3 placebo-controlled studies		
PIPF-004 (IPF)	Total: 435	
	Pirfenidone 2403 mg/d: 174	Pirfenidone 2403 mg/d: 70.7 weeks (2-104 weeks)
	Placebo: 174	Placebo: 71.4 weeks (<1-110 weeks)
	Pirfenidone 1197 mg/d: 87	Pirfenidone 1197 mg/d: 73.0 weeks (13-109 weeks)
PIPF-006 (IPF)	Total: 344	
	Pirfenidone 2403 mg/d: 171	Pirfenidone 2403 mg/d: 75.4 weeks (6-118 weeks)
	Placebo: 173	Placebo: 74.9 weeks (1-120 weeks)
PIPF-016 (IPF)	Total: 555	
	Pirfenidone 2403 mg/d: 278	Pirfenidone 2403 mg/d: 47.5 weeks (2−55 weeks)
	Placebo: 277	Placebo: 49.0 weeks (2−56 weeks)
Ongoing uncontrolled Phase 2 study		
PIPF-002 (IPF/PF) Cutoff: 07 August 2013	Total: 83 Pirfenidone 2400 to 3600 mg/d: 83	Pirfenidone: 167.1 weeks (3−519 weeks)
Ongoing uncontrolled Phase 3 extension study		
PIPF-012 (IPF) Cutoff: 07 August 2013	Total: 603 Pirfenidone 2403 mg/d: 603	Pirfenidone: 149.4 weeks (1−257 weeks)

Note: All patients had a diagnosis of IPF with the exception of 2 patients in PIPF-002.

The 'Randomised patient subset' was the 2,403 mg/day pirfenidone (n = 623) and the placebo groups (n = 624) from PIPF-004, PIPF-006, and PIPF-016. Overall the demographics across treatment groups were well balanced. Most of the information below focuses on information from this subset.

The 'Pirfenidone patient subset' additionally included patients from PIPF-002 and PIPF-012, and those treated with pirfenidone 1,197 mg/day in PIPF-004 (total n = 1067, n = 980 treated with 2,403 mg/day pirfenidone dose).

Long-term exposure in clinical studies included 172 patients treated for at least five years.

Table 7. Exposure to pirfenidone 2,403 mg/day in clinical studies, according to duration

Contributing Study	Randomized Patient Subset			Pirfenidone Patient Subset
	Pirfenidone 1197 mg/d	Pirfenidone 2403 mg/d	Placebo	
Phase 3 placebo-controlled studies				
PIPF-004	87[a]	174	174	261
PIPF-006	0	171	173	171
PIPF-016	0	278	277	278
Ongoing uncontrolled Phase 2 study				
PIPF-002	0	0	0	83
Ongoing uncontrolled Phase 3 extension study				
PIPF-012	0	0	0	274[b]
Total	87[a]	623	624	1067

[a] Pirfenidone 1197 mg/d group not included in Randomized Patient Subset, but included in Pirfenidone Patient Subset

[b] PIPF-012 includes 603 patients, but only 274 are newly exposed to pirfenidone, having been randomized to placebo in PIPF-004/PIPF-006

Table 8. Summary of Patient-Exposure years

Duration on Study Treatment	2009 ISS		Additional Data		Cumulative Data	
	Pirfenidone (N = 345)	Placebo (N = 347)	Pirfenidone (N = 278)	Placebo (N = 277)	Pirfenidone (N = 623)	Placebo (N = 624)
Duration on study treatment (months)						
n	345	347	278	277	623	624
Mean	16.8	16.8	10.9	11.3	14.2	14.4
Standard deviation	5.19	4.94	2.65	2.29	5.15	4.85
Median	16.9	16.7	12.0	12.0	12.3	12.5
Min, Max	>0, 27	>0, 28	>0, 13	>0, 13	>0, 27	>0, 28
Number of patients on study treatment, n (%)						
>0 to <3	13 (3.8)	8 (2.3)	9 (3.2)	7 (2.5)	22 (3.5)	15 (2.4)
3 to <6	14 (4.1)	15 (4.3)	16 (5.8)	9 (3.2)	30 (4.8)	24 (3.8)
6 to <9	11 (3.2)	12 (3.5)	15 (5.4)	11 (4.0)	26 (4.2)	23 (3.7)
9 to <12	5 (1.4)	7 (2.0)	128 (46.0)	122 (44.0)	133 (21.3)	129 (20.7)
12 to <15	11 (3.2)	8 (2.3)	110 (39.6)	128 (46.2)	121 (19.4)	136 (21.8)
15 to <18	152 (44.1)	170 (49.0)	0	0	152 (24.4)	170 (27.2)
18 to <21	66 (19.1)	66 (19.0)	0	0	66 (10.6)	66 (10.6)
21 to <24	66 (19.1)	49 (14.1)	0	0	66 (10.6)	49 (7.9)
≥24	7 (2.0)	12 (3.5)	0	0	7 (1.1)	12 (1.9)
PEY[a]	482.7	486.7	253.0	260.1	735.7	746.8

[a] One person exposure year (PEY) is equal to 1 patient exposed to study drug for 1 year (ie, 365.25 days). The total of the PEYs is the sum of all patients' PEYs in that treatment group and data view.

The majority of patients (64%) had a mean daily dose of pirfenidone > 2200 to ≤ 2600 mg/day.

Safety issues with the potential for major regulatory impact

Several issues identified during drug development and with subsequent experience have implications for safe use.

Liver toxicity

Pirfenidone has a known association with liver toxicity. Hepatic events were analysed in the cumulative datasets as adverse events of interest, for example through SMQ 'possible drug-related hepatic disorders-comprehensive search'. Liver related laboratory outcomes

were categorised according to specified test range values, as described in the 2012 Safety Update SAP for the assessment of potential hepatotoxicity.

In the randomised patient subset 9.5% pirfenidone patients reported hepatic TEAEs versus 4.3% for placebo. There were 6 pirfenidone patients with hepatic treatment emergent (TE) serious adverse events (SAEs) versus 1 placebo patient. Three pirfenidone patients had moderate to severely abnormal LFTs judged probably related and 2 had severe hepatitis, judged probably or possibly related. One was discontinued because of persistent GGT elevation and diagnosed with malignant hepatic neoplasm. Overall LFT elevations were more frequent and severe with pirfenidone treatment.

Notable elevations in aspartate transaminase (AST)/alanine transaminase (ALT) tended to occur early in therapy; of 21 patients with an ALT /AST > 3 x the upper limit of normal (ULN), 14 first had ALT/AST > 3 x ULN in the initial 6 months of treatment. Of 7 pirfenidone patients with ALT/AST > 5 x ULN, 5 patients first had that elevation in the first 6 months; 2 patients had smaller elevations (Grade 1, mild, up to 3 x ULN) at Baseline and during the initial 6 months of treatment. For ALT/AST >3 and < 5 x ULN (in the absence of symptoms or bilirubin > 2 x ULN), the protocols allowed dose reduction or interruption if clinically appropriate, with subsequent re-titration to full dose, as tolerated. Of 15 patients in this category 12 were on pirfenidone at completion of study, 7 on full dose.

Data from the pirfenidone patient subset indicated that adjusted incidence rates did not increase with longer term exposure.

In the combined database, including Japanese Phase II studies, PIPF-016 and 2-market reports (total exposure approximately 15,000 patients), 4 patients met Hy's law criteria of concomitant elevations in ALT or AST > 3 x ULN and total bilirubin > 2 x ULN in the absence of alternate explanations. In all 4 cases, liver test elevations occurred early after first exposure to pirfenidone (that is ALT > 5 x ULN by Week 13), and all showed reversal after discontinuation of pirfenidone.

Regular LFT monitoring was useful for early identification and new onset symptoms such as nausea, abdominal discomfort or malaise should be considered as a warning for potentially serious LFT elevations. LFT evaluation is therefore recommended prior to initiation of therapy and then monthly for the first 6 months and 3 monthly thereafter.

Evaluator's comment: Advice from the Phase III study protocols is the basis of the PI recommendations for managing drug dosage with elevation of LFTs. The sponsor's recommendation in 2014 RSU are:

LFTs 3-5 x ULN, bilirubin normal; cease confounding medications and monitor closely, and interrupt or reduce and titrate pirfenidone as necessary.

LFTs 3-5 x ULN with symptoms or elevated bilirubin; permanently discontinue.

ALT/AST > 5 x ULN; permanently discontinue.

Haematological toxicity

There were occasional reports of haematological abnormalities in the clinical development program. There were 3 reports of SAE of agranulocytosis in the post-marketing experience (as of 28 February 2014). Each event occurred within 2 months after the start of pirfenidone treatment. Each patient's neutrophil count normalized when pirfenidone was discontinued.

Serious skin reactions

Photosensitivity reaction was reported for 9.3% of pirfenidone patients and 1.1% of placebo patients in the randomised patient subset, most within the initial 6 months. In the pirfenidone group, one patient had a TE SAE. Rash was reported for 30.3% of pirfenidone patients (1 patient had a SAE) and 10.3% of placebo patients. The narratives for patients

with individual skin SAEs were not accessible. The PI notes that patients must be protected from sunlight.

Cardiovascular safety

In cumulative data for the randomised patient subset there was an imbalance in cardiac arrhythmias (pirfenidone14.4% versus 8% placebo) and valvular incompetence (1.1% versus 0.6%; 1 SAE of mitral valve incompetence in a patient on pirfenidone). Types of arrhythmia events were diverse and numbers were low for specific events. The pirfenidone group recorded 1 death (myocardial infarction) versus 4 deaths from cardiac disorders in the placebo group, with an additional death in the placebo group assessed by MAC as sudden cardiac death. In the cumulative pirfenidone patient subset 13 additional cardiac deaths were identified in the long-term safety studies PIPF-002 and PIPF-012, all with a medical history of cardiac disease or risk factors prior to pirfenidone treatment.

Review by independent cardiology experts concluded that there was no clear evidence of an effect of pirfenidone on heart rate, cardiac depolarization, QT prolongation, or electrocardiographic morphology.

Unwanted immunological events

There were 14 reports of angioedema in the post-marketing experience (as of 28 February 2014). All occurred within 3 months after the start of pirfenidone treatment. A majority of the cases were considered serious but each patient improved when pirfenidone was discontinued.

Post-marketing data

Seven PSURs were provided. The cumulative post-marketing exposure as of 27 February 2014 was estimated to be 13,191 patient years, a total of approximately 15,000 patients.

PSUR 4 included the case of elevated bilirubin in PIPF-016 that triggered review of hepatic events. Three other cases of Hy's law were found as described below. Increased total serum bilirubin in conjunction with elevated AST and ALT was added to the Summary of Product Characteristics (SPC).

Based on reports in PSUR 5 and PSUR 6, as of 28 February 2014, two new TEAEs of interest were identified in post-marketing experience, added to the SPC and assessed as safety signals for pirfenidone:

- Agranulocytosis (3 cases identified)

- Angioedema (14 cases identified).

According to PSUR 7, up until 27 August 2014 the estimated cumulative exposure in clinical trials was 1574 patients and total post-marketing exposure was estimated to be 16,634 patient-years. There are named patient programmes and patient assistance programmes in Europe and patient registries in both Canada and the Benelux. A post-authorisation safety Study PIPF-025 has enrolled approximately 1,000 participants. Since the international birth date (IBD) of 28 February 2011, a total of 8185 suspected ADRs have been reported in the post-marketing surveillance period. This included 1931 (23.6%) from spontaneous reporting, literature, or regulatory authorities; 190 (2.3%) from clinical trials; and 6064 (74.1%) from solicited reporting. The majority (7161) were non-serious. The total number of ADRs increased from 5525 in PSUR 6 to 8185 in PSUR 7. This is stated to be largely due to solicited reporting and spontaneous post-marketing reports from Europe and Canada.

Overall the pattern of the post-marketing AEs is similar to that observed in clinical trials.

In PSUR 7 a series of cases of thrombocytopenia were reported in post-marketing surveillance. These cases lead to an investigation of thrombocytopenia as a safety signal.

The MAH concluded that current information was not sufficient to propose any current changes to the reference safety information and that more monitoring of this signal would be required. Additionally there was mention of a potential warfarin-pirfenidone interaction.

Evaluator's conclusions on safety

Overall the data indicated a well characterised and acceptable safety profile for IPF patients, although monitoring and effective management of adverse events will be required. Dose adjustments may be needed soon after initiation and this is important for the proposed usage.

Occurrence of common AEs such as GI and CNS responses may be amenable to measures to improve tolerability, such as dose escalation and dosing with food as recommended in the PI. Dose reduction or interruption might be required to allow recovery and subsequent dose titration. Some AEs require prompt assessment to avoid serious clinical consequences. The onset of an adverse event needs to be recognised as a potential reaction to pirfenidone that might require discontinuation or dose reduction.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of pirfenidone in the proposed usage in patients with IPF include:

- Reduction in the decline of percent predicted FVC

- increased proportion of patients with improved exercise tolerance, (for example 6-MWT)

- in pooled analyses, suggestion of reduction in mortality.

First round assessment of risks

The risks of pirfenidone in the proposed usage are:

- Well characterised GI, CNS and hepatic adverse events that can generally be managed in clinical practice

- drug interactions.

First round assessment of benefit-risk balance

The benefit-risk balance of pirfenidone, given the proposed usage, was deemed favourable at Round 1 by the clinical evaluator.

First Round Recommendation Regarding Authorisation

At Round 1, recommendation for registration of pirfenidone for IPF was expected, subject to satisfactory responses to questions (see clinical questions below) and satisfactory amendments to the PI (details of which are beyond the scope of this AusPAR).

Clinical Questions

Additional expert input

The following aspects are inconsistent across international regulatory agencies and need resolution prior to Australian approval:

- Is the narrower Indication for the treatment of 'mild to moderate' IPF appropriate, as per the SPC?

- Should use be contraindicated in severe hepatic and renal disease as in the SPC?

Clinical questions for the sponsor

1. The Indication approved by the EMA is for the treatment of *'mild to moderate Idiopathic Pulmonary Fibrosis'*.

    a. Please provide the location of the justification for the widening the target population for the Australian submission to treatment of all stages of IPF severity.

    b. Please provide any available information on clinical efficacy outcomes in Australian patients provided with pirfenidone 'Esbriet' through the SAS.

2. The proposed Indication does not specify *'mild to moderate IPF'*. However, use of pirfenidone in severe stage IPF is described as '*missing information'* in the Safety Specification in the draft RMP.

Please clarify this inconsistency.

3. Please provide PSUR 8 which should be available, covering the period to August 2014 to February 2015.

4. Have there been regulatory actions with respect to thrombocytopenia or warfarin interaction signals?

5. Please provide any available information on safety in Australian patients provided with pirfenidone 'Esbriet' through the SAS.

Second Round Evaluation of clinical data submitted in response to questions

Inconsistencies between EMA and Australian proposed indication

The sponsor confirmed that the widening of the indication to all stages of IPF severity is consistent with the data provided for FDA approval, due to the modification of the entry criteria in Study PIPF-016 to favour enrolment of patients with a greater likelihood of disease progression. These are the same data provided with this submission. This is acceptable.

Australian clinical efficacy outcomes

The sponsor replied that information collected in association with supply under SAS does not include efficacy data. This is acceptable.

Potential inconsistency in safety specification in the draft RMP

In response regarding inconsistency between the proposed indication RMP description of use in severe stage IPF as 'missing information', the sponsor explained further that this was due to the indication approved in EU. A post-authorisation commitment to address the potential risk of missing data, approved by EMA CHMP, was undertaken by conducting the post-authorisation safety study, the registry study 'PASSPORT' (PIP-025) to evaluate the long-term safety profile. The approximately 1,000 patients already registered have a Baseline FVC range from 21% to 121%, median 64.7% and 143 patients have Baseline FVC < 50%.

PSUR 8 availability

As of this PSUR reporting period, estimated cumulative patient exposure to pirfenidone in clinical trials was 1574 patients. Cumulative post-marketing exposure was estimated to be 20,368 patient years. During this six month reporting period, the total worldwide post-marketing exposure to pirfenidone was estimated to be 3743 patient years. In this PSUR reporting period, 7651 suspected ADRs were received. A total of 591 (7.7%) were from spontaneous or literature reports, 47 (0.6%) were from clinical trials, and 7013 (91.7%) were from solicited reporting. The total (cumulative) number of ADRs has nearly doubled from 8185 in PSUR 7 to 15,827 in PSUR 8 largely due to solicited reporting from patient support programme reporting originating in the US.

In PASSPORT to December 2014 there were 670 of 1006 (66.6%) patients who experienced a total of 1790 ADRs of special interest. The safety profile was comparable to the label with the most frequent adverse reactions including gastrointestinal (34.4%) and skin (25.1%) SOCs. Also common was the category 'other clinically significant ADR (28.9%) which included decreased appetite (11%) cough (2.5%) dyspnoea (2.2%) and headache (2.1%).

In PASSPORT there were 55 (5.5%) patients who experienced 77 SADRs. Fifteen of 55 patients (1.5 %) had gastrointestinal disorders, such as diarrhoea, nausea, or vomiting. Ten patients (1.0%) reported a skin or subcutaneous tissue disorder, such as photosensitivity, erythema, or rash; 5 reported weight decreased, 1 of which was fatal with no information to suggest cause of death other than IPF.

Abnormal LFTs. dizziness, fatigue and weight loss are addressed in the PI.

One 18 year old patient who was given Esbriet for lung fibrosis after a double lung transplant developed angioedema and pirfenidone was ceased.

Regulatory actions and thrombocytopenia or warfarin interaction signals

The sponsor stated that these remain as open signals with continued monitoring. There has been no update to the core data sheet (CDS) or EU SmPC. A summary of the PRAC assessment was provided.

It noted 7 reports of thrombocytopenia, potentially confounded, and none in clinical studies.

For warfarin-pirfenidone interaction the EMA rapporteur assessment was no change in relative frequency, and ongoing monitoring was required. The FDA has also asked about this and the sponsor is preparing a draft report. A tabular overview of regulatory actions was provided.

A detailed response is provided in answer to the RMP evaluation.

Information on pirfenidone safety in Australian SAS patients

The Roche SAS safety database identified 2 patients who received Esbriet and experienced adverse events.

The first concerned a female aged > 80 years who developed nausea and vomiting after staring pirfenidone 2,403 mg daily total in 3 separate doses. Vomiting ceased when she ceased the capsules and re-occurred after re-introduction. Nausea and vomiting are known AEs for Pirfenidone and listed in the proposed PI in Table 4 as 'occurring in ≥ 10% Pirfenidone treated patients and more commonly than placebo'.

The second concerned a male aged > 70 years who developed shingles 312 days after initiating treatment, with concurrent conditions including osteoarthritis, hypertension and prostatitis, with concomitant medications treating these conditions. The physician assessed the relationship as unrelated to pirfenidone.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

The benefits of pirfenidone are unchanged from those identified in the First Round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of pirfenidone are unchanged from those identified in the First Round assessment of risks.

Second round assessment of benefit-risk balance

The clinical evaluator considers that based on the available data the benefit-risk balance of pirfenidone 'Esbriet, given the proposed usage, is favourable.'

Second round recommendation regarding authorisation

The clinical evaluator considers that the data provided support registration of pirfenidone for the proposed indication:

> *'Esbriet is indicated for the treatment of idiopathic pulmonary fibrosis (IPF)'.*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 07 (dated 27 October 2014, DLP 27 August 2014) and Australian-specific annex (ASA) Version 1.0 (dated March 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 9.

Table 9: Summary of safety concerns as provided by sponsor

Summary of safety concerns	
Important identified risks	Photosensitivity reaction and rash
	Abnormal liver function tests, increased ALT and AST levels, total serum bilirubin increased in combination with increases in ALT and AST
	Dizziness
	Weight loss
	GI symptoms
	Fatigue
	Angioedema
Important potential risks	Falls
	Specific cardiac events (supraventricular tachyarrhythmia, atrioventricular block/sick sinus syndrome, ventricular arrhythmia, bundle branch block, aortic or pulmonic valvular incompetence
	Increased platelet count
	Off-label use
	Potential drug interactions (including smoking, ciprofloxacin, warfarin)
	Blood dyscrasias
	Severe skin reactions
Missing information	Patients being treated concomitantly with immunosuppressants
	Patients with secondary causes of pulmonary fibrosis
	Patients with pre-existing risk factors for hepatic dysfunction such as alcohol abuse and diabetes
	Patients with pre-existing prolonged QT interval
	Patients with severe underlying cardiac, hepatic or any other form of pulmonary disease
	Patient treated concomitantly with other IPF treatments
	Patients suffering from severe stages of IPF
	Exposure during pregnancy and lactation

RMP evaluator's comment:

Notwithstanding the evaluation of the clinical aspects of the safety summary, there are no definite objections to the list of safety concerns and missing information items provided in the context of this application.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information. These activities are summarised in Table 10.

Table 10: Additional pharmacovigilance activities planned by the sponsor

Additional activity	Assigned safety concern	Actions/outcome proposed	Planned submission of final data
Post-Authorisation Safety Study (PASS) of Esbriet (Pirfenidone): A Prospective Observational Registry to Evaluate Long Term Safety in a Real World Setting	All safety concerns.	The objective of this study is to evaluate the long-term safety profile of Esbriet in patients with IPF and to monitor for any unknown or potential risks of treatment with Esbriet.	Safety Updates to coincide with PSUR timetable (Final report planned Q3 2017)

RMP reviewer's comments in regard to the pharmacovigilance plan and the appropriateness of milestones

There is no definite objection to the pharmacovigilance plan proposed by the sponsor in the context of this application.

Risk minimisation activities

The sponsor proposes routine and additional risk minimisation activities for the EU, but only routine risk minimisation activities for the Australian market. The sponsor has provided a justification for this as follows:

- Information in the EU communication and checklist reflects the EU SmPC however does not have additional information to aid the physician managing the risks of photosensitivity and abnormal liver function

- Educational material will be available at launch and will include direction to review the PI before prescribing. In this way the information regarding these risks is viewed in context.

The additional risk minimisation activities in the EU are for the following safety concerns:

- Photosensitivity reaction and Rash

- Abnormal liver function tests, increased ALT and AST levels, total serum bilirubin increased in combination with increases of ALT and AST.

The additional risk minimisation activities in the EU consist of the following:

- A safety checklist for all medical staff about monitoring and management of photosensitivity reaction and rash

- A safety checklist for all medical staff about monitoring and management of hepatic related events including asymptomatic abnormal levels of ALT/AST.

RMP evaluator comment

It is desirable that the risk minimisation activities in Australia are equivalent to the risk minimisation activities in the EU. It is recommended that the sponsor provide a Dear Health Care Professional Letter (DHCPL) to the relevant group of prescribers. This DHCPL should include the same information as the activities in the EU.

Reconciliation of issues outlined in the RMP report

Table 11 below summarises the first round evaluation of the RMP, the sponsor's responses to issues raised and the RMP evaluator's evaluation of the sponsor's responses.

Table 11: Summary of RMP recommendations with sponsor's responses and RMP evaluator's comments

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	Safety considerations raised in the evaluation reports have been included as appropriate in updated RMP.	The sponsor's response has been noted.
Any ASA updates should be provided in the current ASA format.	Esbriet ASA v1.1 has been updated to the current TGA ASA format as requested.	The sponsor's response has been noted.
The sponsor should provide a summary of the post-market experience with overdose.	Limited data are available on over dosage in humans. The highest dose studied in healthy volunteers was 4,806 mg/day (PIPF-008). Adverse reactions observed due to multiple doses of pirfenidone up to dose of 4,806 mg/day were mild, transient, and consistent with the most frequently reported adverse reactions for pirfenidone. An advice on providing supportive medical care has been included in reference safety information. Treatment of overdose with pirfenidone consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. It is unknown if pirfenidone is dialysable. There is no specific antidote for overdose with pirfenidone. Roche believes that because of the instructions about dosing in the PI the potential risk of either	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	accidental or intentional overdose is very low.	
	As part of Roche's response, a cumulative review of the safety database was performed.	
	Cumulatively, 214 patients were identified using these broad search criteria. Of the 214 cases:	
	134 Cases involved patients not consistent with medical concept of overdose including drug dose omission, intentional under doses and were excluded from further analysis of the medical concept of overdose.	
	The remaining 80 cases were then reviewed to identify cases consistent with the medical concept of pirfenidone overdose:	
	Of these 80 cases, 55 were reviewed and assessed as not being consistent with the medical concept of pirfenidone overdose. Events in this group included experiencing issues related to dose escalation, skipping doses and overdose with use of narcotics, digoxin.	
	Of the 80 cases, the remaining 24 cases were then reviewed:	
	• Of these 24 cases, 13 had very limited clinical information with which to fully assess. In these 13 cases, the sequence of events is unknown and there is no additional available information to assess	
	• Of these 24 cases, 11 cases had some clinical information and had events consistent with the medical concept of pirfenidone overdose.	
	• Eleven cases had some clinical information and had events potentially consistent with the medical concept of pirfenidone overdose. The reporting sources for these 11 cases were clinical study (1), spontaneous (5), and Non-Interventional Study/Program reports (5). Of the 11 cases, 5 were medically confirmed and 6 were not medically confirmed. The gender reported was female in 4 cases and male in 7 cases. The reported age of the patients ranged from 64 to 82 years. The indication, in all 11 cases included IPF. The PTs for the events consistent with the medical concept of pirfenidone overdose included the PTs Overdose (4), Accidental overdose (3), Intentional product misuse (1), Extra dose administered (1), Intentional overdose (1), Intercepted medication error (1).	
	Of these 11 cases:	
	• Nine cases describe taking outside the prescribed dosing frequency posology or a	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	nonspecific report of overdose (dose unknown).	
	• Reported symptoms in the cases include - no adverse event, dizziness, headache, no appetite, bruises easily, sluggishness, and heartburn. All were managed with supportive care.	
	• Only two cases involved taking a daily dose above a total of 9 capsules /day (2,403 mg/day):	
	In [information redacted] the event of Intentional overdose occurred when the patient argued with his wife and afterwards took 57 tablets of Pirespa and 45 tablets of cilostazol. The patient's concurrent medical conditions included arteriosclerosis obliterans, benign prostatic hypertrophy, and a current tobacco user. Concomitant medications included cilostazol, silodosin, and tamsulosin hydrochloride. The patient was also started on lansoprazole. The patient was on oxygen therapy. The patient developed mild disturbed consciousness and was admitted to the hospital. Approximately 13 days later, the patient recovered from the event of psychiatric symptom (excessive dose administration). On an unknown date, the event of disturbed consciousness resolved without sequelae 'with only infusion solution' and the patient was discharged from the hospital.	
	[Information redacted] concerns a female patient of unknown age patient who was confused by prescription label and took 9 capsules in each morning, midday and evening. On an unknown date, she experienced a sharp pain in the stomach. It was stated that, it was happened before or while she was moving around. Later, sharp pain in stomach resolved. Later, she had skin issues which aggravated on exposure to sun. She used the aloe that came with her prescription but cannot find the sunscreen. On an unspecified date, she experienced rash that she believed to be associated with sun exposure, on the top of her hands and ankles where she hasn't been putting SPF 50 sunscreen (photosensitivity rash) and itching that woke her up at night. The outcome of skin issues, photosensitivity rash and itching was not reported and it was not known whether the therapy with pirfenidone ongoing or not.	
	The cumulative patient–year exposure to pirfenidone is, as of PSUR 8, 20,368 patient–years. A cumulative review of the Esbriet safety database to identify overdose events was performed. This review only identified a limited number of patients identified as having experienced overdose with pirfenidone. Most of those patients	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	received doses at a schedule outside prescribed and were managed with supportive care. Only two patients were identified who had a daily dose above 9 capsules /day (2,403 mg/day). In both cases the overdose was able to be managed with general supportive measures. Roche considers that this cumulative review of pirfenidone overdose is consistent with the current labelling and the information in the RMP.	
It is desirable that the risk minimisation activities in Australia are equivalent to the risk minimisation activities in the EU. It is recommended that the sponsor provide a DHCPL to the relevant group of prescribers. This DHCPL should include the same information as the activities in the EU.	Roche acknowledges this request and will implement equivalent risk minimisation activities in Australia as those implemented in Europe that is, provide a DHCPL at launch.	The sponsor's response has been noted. The draft materials should be provided to TGA before approval/launch.
The sponsor should provide a report of the measures to assess the effectiveness of the currently undertaken risk minimisation activities in the EU.	The additional risk minimization measures (educational materials) included in Annex 11 of the RMP are required to be distributed at the time of launch in each EU country. Roche can confirm that studies to measure the effectiveness of the currently distributed educational materials in the EU have not been undertaken either by Roche or by the former MAH.	The recommendation remains. The sponsor should provide relevant reports of the measures to assess the effectiveness of the currently undertaken risk minimisation activities in the EU, once they become available.
In the 'Precautions' section, the PI should include information on cardiovascular events observed with Esbriet and a recommendations to monitor for them.	The occurrence of cardiac TEAEs in the categories of arrhythmia, conduction disorders, or valvular abnormalities is to be expected in an older patient population with pulmonary disease and a high prevalence of underlying cardiovascular disease. For cardiac TEAEs of interest, the cumulative data are generally consistent with those of the 2009 Integrated Summary of Safety. In the 2014 cumulative data, a larger proportion of pirfenidone patients than placebo patients had a TEAE in the cardiac arrhythmia SMQ (14.4% pirfenidone versus 8.0% placebo). However, the types of events were diverse, and no type of	This is considered acceptable at this stage in the context of this application for RMP purposes, subject to Delegate approval.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	arrhythmia predominated. Reviews of the data by two independent, external experts concluded that there is no clear evidence of an effect of pirfenidone on heart rate, cardiac depolarization, QT prolongation, or electrocardiographic morphology, and that the profile of events is inconsistent with the effect of a drug on cardiac rhythm. Furthermore, the ECG study (PIPF-007) and the findings of nonclinical studies of pirfenidone do not suggest an effect on cardiac rhythm. Therefore Roche do not propose to include any statements in the Esbriet PI, this is in line with the EU SmPC and the US PI.	
In the 'Precautions' (or 'Adverse Events') section, the PI should, under separate headings include information on angioedema, fatigue, dizziness (with reference to a potential risk of falls), and weight loss (with reference to monitoring of weight). This is recommended to align the Australian PI with the list Important Identified Risks in the Safety Specification and also the EU SmPC.	Text has been proposed for the Esbriet PI to align with the EU SmPC as requested.	This is considered acceptable at this stage in the context of this application for RMP purposes, subject to Delegate approval.
In the 'Contraindications' section, the PI should include severe hepatic impairment/end stage liver disease and severe renal impairment/end stage renal disease as contraindications.	Text has been proposed for the Esbriet Product Information as requested.	This is considered acceptable at this stage in the context of this application for RMP purposes, subject to Delegate approval.
In the 'Interactions with other medicines' section, the PI should include the known information on the interaction with warfarin.	[Further text from sponsor's response not reproduced here] In summary, the issue of INR variability in both the general patient populations on warfarin and in the INR test itself is well documented over many years in the scientific literature. Conclusion Given the inconsistency of change in INR in the safety database, the clinical information, in the scientific literature, regarding the issue of INR	This is considered acceptable at this stage in the context of this application for RMP purposes, subject to Delegate approval.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	variability in both the general patient populations on warfarin and in the INR test, Roche has confirmed that there is no need at this time to amend the CDS, the RMP, or the prescribing information.	
In the 'Overdose' section, the PI should include the known information with overdose.	Text has been proposed for the Esbriet PI as requested.	This is considered acceptable at this stage in the context of this application for RMP purposes, subject to Delegate approval.
It is recommended to the Delegate that the draft CMI document be revised to accommodate the changes made to the PI document.	Text has been proposed for the Esbriet CMI to reflect the proposed changes to the Esbriet PI.	This is considered acceptable at this stage in the context of this application for RMP purposes, subject to Delegate approval.

Summary of recommendations

Outstanding RMP issues

1. The draft education materials should be provided to TGA before approval/launch.

2. The sponsor should provide relevant reports of the measures to assess the effectiveness of the currently undertaken risk minimisation activities in the EU, once they become available.

3. The educational material for Australia should adapt the warning with regard to photosensitivity to the Australian context (specifically in relation to the increased sun exposure).

4. It would be desirable to include Australian patients in the conducted registry study to obtain photosensitivity data in the Australian context.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

The committee noted the following safety concerns:

- Important identified risks: photosensitivity reaction and rash; abnormal liver function tests, increased ALT and AST levels, total serum bilirubin increased in combination with increases of ALT and AST; dizziness; weight loss; gastrointestinal symptoms; fatigue; angioedema

- Important potential risks: falls; specific cardiac events (supraventricular tachyarrhythmia, atrioventricular block/sick sinus syndrome, ventricular arrhythmia, bundle branch block, aortic or pulmonic valvular incompetence); increased platelet

count; off-label use; potential drug interactions (including smoking, ciprofloxacin, warfarin); blood dyscrasias; severe skin reactions

- Missing information: patients being treated concomitantly with immunosuppressants; patients with secondary causes of pulmonary fibrosis; patients with pre-existing risk factors for hepatic dysfunction such as alcohol abuse and diabetes; patients with pre-existing prolonged QT interval; patients with severe underlying cardiac, hepatic or any other form of pulmonary disease; patients treated concomitantly with other IPF treatments; patients suffering from severe stages of IPF; exposure during pregnancy and lactation.

In addition to the information presented in the agenda papers, the committee referred to a paper by Noble et al.[32]

The committee provided advice on specific questions relating to the RMP.

1. *Can the committee comment on the adequacy of the proposed risk minimisation plan for Australia which does not contain the same activities (such as prescriber checklists) as conducted in the European Union (EU). If not considered adequate, can the committee advise which additional activities might be required?*

The additional risk minimisation activity required in the EU is that the sponsor is required to provide an educational programme for physicians, prior to launch, aiming to provide educational material on the correct prescription of pirfenidone. The education is to include a safety checklist for all medical staff about:

- monitoring and management of photosensitivity reaction and rashes monitoring
- management of hepatic related events including asymptomatic abnormal levels of ALT /AST.

Photosensitivity reaction was reported for 9.3% of pirfenidone patients and 1.1% of placebo patients. The committee noted that medicines causing photosensitivity of a similar order of magnitude (for example ciprofloxacin) are in use without a prescriber's safety checklist specific to this adverse event.

Overall, the committee advised that there is no obvious reason that strategies to be implemented in the EU, including mail outs to healthcare practitioners, would not also be appropriate in Australia. The use of safety checklists would be a useful contribution to the safety profile of the medicine, particularly where the patient is not being managed by a specialist respiratory physician.

Given the tropical latitudes and sun exposure common in Australia, it will be useful to monitor photosensitivity and rash in the Australian context. It would also be useful to extract from the clinical trials data information on the experience of Australian patients regarding photosensitivity and rashes. The committee noted that the prospective observational registry study to evaluate long-term safety is being conducted only in the EU.

IPF is confined to the lungs. The committee proposed that consideration be given to mandating that only respiratory physicians can initiate the prescribing of pirfenidone. While this proposal is not to address a particular safety concern, it would ensure that patients with IPF are treated by highly specialised healthcare practitioners who can consider the widest range of therapeutic options.

Other comments:

---

[32] Noble PW et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377:1760-1769.

The committee noted that the proposed indication for pirfenidone is 'treatment of idiopathic pulmonary fibrosis' whereas the EU approved indication is 'treatment of mild to moderate idiopathic pulmonary fibrosis'.

The committee noted the safety summary of the medicine and the Post Authorisation Safety Study (PASS) proposed to address the safety concerns and missing information. Inclusion of 'patients treated concomitantly with other IPF treatments' as 'missing information' was notional, as at this time IPF is treated by supportive care only.

Suggested wording for conditions of registration

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

Implement EU-RMP Version 7.2 (dated 27 July 2015, DLP 27 February 2015) and Australian-specific annex (ASA) Version 1.1 (dated 30 October 2015) and any future updates, where TGA approved, as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was considered and summarised by the Delegate as follows:

Background

Pirfenidone is an immunosuppressant; the mechanism of action has not been fully established. However, the sponsor proposes its anti-inflammatory and anti-fibrotic effects as the mechanism of action for pirfenidone. It is approved for treatment of IPF in other countries including the EU, USA and Canada. It is available through SAS (for experimental drugs) in Australia.

Nintedanib was recently approved by the TGA for treatment of IPF in Australia is also approved in the USA.

Quality

The quality evaluator recommended against registration because: '*the proposed limit of NMT 0.05% for the impurity D in the drug substance has not been qualified.[3] The specified impurity is a clastogenic impurity and considered to pose a carcinogenic risk above that normally considered acceptable for human pharmaceuticals. On the basis of the toxicological advice, the permitted daily exposure limit for the specified impurity in pirfenidone drug substance is 133 µg/day for the maximum recommended dose of 2,403 mg of pirfenidone daily. This corresponds to a maximum limit of 0.0055% of the specified impurity in the drug substance.*' No data has been provided to demonstrate that the qualified limit of NMT 0.0055% for the specified impurity in the drug substance can be met. The evaluator states that the sponsor has been informed of ways to address these issues.

A food effect study, PIPF-005 is discussed. This was a single dose and multi dose bioavailability study. Only the single dose aspect is evaluated by the quality evaluator. The evaluator states that food significantly reduced the rate of absorption. Though the multi dose aspect of the study has not been evaluated by the quality evaluator, an observation is made, '*that the study indicated that both pirfenidone and the 5-CA-pirfenidone metabolite showed decreased clearance with increasing dose given. Oral clearance is saturable with increasing dose, particularly at above 2,403 mg/day, which has been set as the maximum recommended daily dose.*' The quality evaluator questions whether the maximum daily dose is acceptable.

All other outstanding chemistry and quality control issues had been satisfactorily addressed. This submission has not been considered by PSC.

Nonclinical

The nonclinical evaluator mentioned that though the mechanism of action has not been fully established, the primary pharmacology data indicate anti-inflammatory and anti-fibrotic activity. Pirfenidone attenuated and/or arrested fibrosis development in an animal model of pulmonary fibrosis, but did not reverse established fibrosis.

Safety pharmacology studies revealed adverse CNS effects in mice with subclinical doses of pirfenidone. Convulsions, respiratory inhibition and mortality were seen at doses of around twice the MRHD based on mg/m^2 body surface area. The evaluator states that, '*reduced blood pressure and increased heart rate occurred in anaesthetised rats and dogs, but only increased heart rate was observed in conscious dogs and at higher doses (14 x C$_{max}$). There were no adverse respiratory effects in conscious dogs at doses yielding up to 4 x the expected C$_{max}$. In vitro and in vivo studies indicated that delayed gastric emptying and reduced rate of intestinal transit are likely to occur clinically*'.

The pharmacokinetic profile of pirfenidone was similar between animals and humans.

In vitro, protein binding at a concentration of 100 μg/mL approximated 30% in the mouse and the rat while in the dog and human it approximated 50%. Tissue distribution studies provided little evidence to suggest accumulation of pirfenidone and its metabolites in any tissues; adequate exposure was shown in the presumptive target organ, the lung. CYP1A2 was the predominant CYP isoform responsible for metabolism, involving formation of the one major metabolite, 5-CA-pirfenidone. The metabolite profile of pirfenidone was qualitatively similar between laboratory species and humans with the major circulating metabolite being 5-CA-pirfenidone. Excretion was predominantly via the urine, almost exclusively as 5-CA-pirfenidone.

Single dose toxicity studies in mice, rats and dogs indicated a relatively low order of acute toxicity for pirfenidone by the oral route.

Repeat dose toxicity studies were conducted in mice (3 months, PO), rats (up to 6 months, PO and IV) and dogs (up to 9 months, PO). These toxicities were observed at low or subclinical exposures (relative exposures, ≤ 3 x based on AUC), but were reversible.

All the genetic toxicology studies were negative and neither pirfenidone nor the 5-CA metabolite is genotoxic.

Fertility was not significantly affected in rats. Pirfenidone and its metabolites were excreted in the milk of lactating rats. Pirfenidone was not found to be teratogenic in rats or rabbits. However, abortion, maternal death, prolonged gestation, reduced pup numbers and viability were observed at estimated relative doses of less than 4 x the MRHD (mg/m^2).

Pirfenidone was phototoxic in hairless mice and Hartley guinea pigs. Pirfenidone potentiated the development of erythema in response to UV exposure at subclinical exposures (C$_{max}$).

Long-term carcinogenicity studies were conducted in mice and rats. Pirfenidone induced hepato-carcinogenesis in both mice and rats, as well as thyroid tumours in rats. These appeared to be secondary to liver enzyme induction. Treatment related uterine tumours also occurred in rats. The evaluator states that the sponsor proposed a rodent specific prolactin mediated mechanism for uterine tumour development, but the mechanistic data provided were insufficient to conclusively support this hypothesis. However, the European Public Assessment Report (EPAR) states that, '*the pirfenidone related liver tumours in rats and mice, and uterine tumours in rats, appear to be rodent and species*

specific and of questionable clinical relevance'. These uncertainties are adequately addressed in the draft PI.

The evaluator expressed concern about the presence of a specified impurity in the drug substance, which is genotoxic (clastogenic) and is considered to pose a carcinogenic risk above that normally considered acceptable for human pharmaceuticals. It is recommended that the limit be lowered to acceptable levels so as to not expose patients to unnecessary risks.

Overall, the nonclinical evaluator recommended approval from a toxicological point of view, provided that the concern regarding the impurity is addressed. Several PI amendments were also made.

Clinical

Pharmacology

In total there were 6 clinical pharmacology studies available, including 5 that provided pharmacokinetic data and a PD study and one population pharmacokinetic analysis.

Pharmacokinetics

The pharmacokinetic data for pirfenidone in healthy subjects was available from Study PIPF-005, with the following pharmacokinetics endpoints obtained:

- After ingestion of single dose of 801 mg (n = 16 with food) pirfenidone had mean peak plasma concentration of 7.8 µg/mL about 3 to 4 hours following administration

- For the 801 mg TDS (2,403 mg/day) dose level, C_{max} was 11.85 µg/mL using data from the multiple dose cohort in PIPF-005; T_{max} (median) was at about 2 hours, t½ was 1.5 h (mean) and the apparent terminal half-life was mean 2.39 h

- Bioavailability was high being approximately 80%. Absolute bioavailability was not determined.

- Food reduced the rate and extent of absorption (C_{max} reduced by 50%, $AUC_{(0-72)}$ by 15 to 20%) compared to fasting state, with subjects less likely to experience adverse events when pirfenidone was administered with food

- No significant dose dependency was identified suggesting linear pharmacokinetics up to a dose of 600 mg TDS

- Mean apparent oral steady-state volume of distribution was approximately 70 L in subjects from Study PIPF-004 (PIPF-ORD1)

- Pirfenidone binds to human plasma proteins, primarily to serum albumin. The overall mean binding ranged from 50% to 58% at concentrations observed in clinical studies (1 to 100 µg/mL)

- There were three metabolites identified in the human studies. None were found to be active.

- The EPAR (for pirfenidone) states that:

  'Following single dose administration of pirfenidone in healthy older (50 to 66 years) adults, the mean apparent terminal elimination half-life was 2.4 hours (PIPF-005). Pirfenidone is predominantly (80 to 85%) excreted via the urine with 95% as the primary metabolite, 5-CA-pirfenidone (PIPF-005)'.

The pharmacokinetics in the targeted population was discussed. The evaluator states that hepatic impairment was likely to be of clinical significance. Study PIPF-011 demonstrated that the AUC between normal subjects and those with hepatic impairment were statistically significantly different. Monitoring of LFTs and recommendations for dose adjustment or treatment discontinuation for elevated LFTs and/or hepatic symptoms is given in the proposed PI.

Study PIPF-009 examined the pharmacokinetics in renal impairment.

Although pirfenidone clearance was not primarily renal, a metabolite 5-CO-pirfenidone was eliminated through the renal pathway. Based on this, the statement, 'use with caution for mild, moderate or severe renal impairment, and not recommended for ESRD' is proposed in the PI.

Population pharmacokinetic analysis did not reveal clinically significant age related differences.

The clinical evaluator states that Study PIPF-101 and Study PIPF-017 assessed pharmacokinetic interactions. The following were observed:

> 'Co-administration of pirfenidone and fluvoxamine (a strong inhibitor of CYP1A2 with inhibitory effects on other CYP isoenzymes (CYP2C9, 2C19, and 2D6)) resulted in a 4-fold increase in exposure to pirfenidone in non-smokers. The exposure to pirfenidone in smokers was 50% of that observed in non-smokers. Smoking has the potential to induce hepatic enzyme production and thus increase clearance and decrease exposure. Co-administration of pirfenidone and 750 mg of ciprofloxacin (a moderate and selective inhibitor of CYP1A2) increased the exposure to pirfenidone by 81%'.

Overall, the clinical evaluator states that the pharmacokinetics have been well characterised with sufficient information to inform the relevant section in the draft PI.

Pharmacodynamics

The clinical evaluator mentions that a PK/PD evaluation in a subset from Study PIPF-004 (n = 88) showed a weak positive relationship between exposure and the primary endpoint of change from Baseline in terms of percent predicted FVC.

Study PIPF-005 showed that higher C_{max} values increased the odds of exposure to a GI adverse event. Study PPF-007 examined the QTc pharmacodynamic potential of pirfenidone in healthy subjects; no significant effect on the cardiac conduction system was seen.

Overall, the evaluator states that PK/PD correlation was demonstrated for common adverse effects including GI and dermatologic adverse events.

Dose ranging studies

There were no formal dose ranging studies conducted. The clinical evaluator states that the 'selection of doses and frequency of administration was based on a published Phase II study in IPF patients that used a maximum dose of pirfenidone 600 mg TDS, and empirical experience generated by investigators in the USA since 1995'.[33]

---

[33] Azuma et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2005 May 1;171(9):1040-7.

Efficacy studies

Three pivotal Studies PIPF-004, PIPF-006 and PIPF-016 were submitted. PIPF-004 and PIPF-006 were similar in design and were the basis of approval in the EMA. Study PIPF-016 was conducted to support the registration in USA, as the former 2 studies were considered inadequate.

Study PIPF-004

Study PIPF-004 was a randomised double blind placebo controlled, three arm study of safety and efficacy of pirfenidone in patients with IPF. The objectives were to assess safety and efficacy of treatment with pirfenidone daily doses of 1,197 mg and 2,403 mg.

Eligible male and female patients aged 40 to 80 years with a confident clinical and radiographic diagnosis of IPF without evidence or suspicion of an alternative diagnosis that may have contributed to the patients' interstitial lung disease, and with evidence of IPF disease progression were eligible for inclusion.

All patients were to receive study treatment from randomisation until approximately 72 weeks after the last patient had been randomised in the study. The treatment dose was to be escalated over 15 days till a full maintenance dose is achieved.

The primary efficacy outcome was absolute change in percent predicted FVC from Baseline to Week 72. PFS was included as a secondary outcome.

Treatments:

1. 1,197 mg/day of pirfenidone administered orally in 3 divided doses (three 133 mg capsules PO TDS for a total of 9 capsules per day) with food.

2. 2,403 mg/day of pirfenidone administered orally in 3 divided doses (three 267 mg capsules PO TDS for a total of 9 capsules per day) with food.

3. Placebo capsules administered orally in 3 divided doses (3 placebo capsules PO TDS for a total of 9 capsules per day) with food.

Sample size calculations are discussed and considered adequate. Statistical testing is discussed, it is noted that differences between the treatment groups and placebo were analysed using rank analysis of covariance (the Mantel-Haenszel mean score chi-square test).

Results; patients (n = 435) were randomised 2: 2: 1 to receive pirfenidone 2,403 mg/day (n = 174), placebo (n = 174), or pirfenidone 1,197 mg/day (n = 87) respectively. Approximately 83% in each group completed the study, (see Table 7 in Attachment 2). In relation to demographics, the clinical evaluator states that, 'mean age was around 66 years in all groups (range 40 to 81); approximately 70% were male, at least 95% were White, and mean BMI was approximately 30 kg/m^2 in all groups. Approximately 66% were enrolled in USA. Other Baseline characteristics were comparable across groups'.

The primary efficacy variable, the difference in percent predicted FVC was statistically significant and reached a maximum absolute difference of 4.8% in favour of pirfenidone at 48 weeks.

The mean change in percent predicted FVC is shown below in Table 12.

Table 12. Comparison of mean change in predicted FVC (percentage) from Baseline at 12 week intervals in pirfenidone and placebo treated cohorts

| Week | Mean Change[a] | | Absolute Difference | Relative Difference | p-value[b] |
	Pirfenidone 2403 mg/d (N = 174)	Placebo (N = 174)			
12	-1.2	-2.7	1.5%	55.6%	0.061
24	-1.4	-3.9	2.5%	64.1%	0.014
36	-2.6	-7.2	4.6%	63.9%	<0.001
48	-4.4	-9.2	4.8%	52.2%	<0.001
60	-6.6	-10.7	4.1%	38.3%	<0.001
72	-8.0	-12.4	4.4	35.5%	0.001

Source: Table 14-2.1.1

[a] For missing values if the patient was alive on the protocol-specified visit, the imputation was by the SSD method. If the patient died on or before the protocol-specified date, then 0 was imputed for the assessment. If the patient was not randomized early enough to have had a particular visit by the end of the study, no imputation was done.

[b] A rank ANCOVA, comparing pirfenidone 2403 mg/d vs. placebo, with standardized ranked change from Baseline as the outcome variable, treatment and geographic region (USA and ROW) as fixed effects, and standardized ranked Baseline as a covariate. Missing data due to a patient's death were ranked as worse than any nondeath and according to time until death.

Secondary efficacy endpoints; the categorical assessment of absolute change in percent predicted FVC reflected the primary variable in showing evidence of treatment effect. Other endpoints did not show statistically significant difference (worsening IPF, PFS rate or 6MWT).

Study PIPF-006

Study PIPF-006 was similar in design and conduct to the previous study, however, it was a two arm study. Patients were randomised 1: 1 to receive pirfenidone 2,403 mg/day or placebo, and were to remain on blinded study treatment from randomisation until approximately 72 weeks after the last patient had been randomised in the study.

Sample size calculations and statistical methods were discussed. The data on FVC were analysed using a rank analysis of covariance (ANCOVA) model with a standardised rank change in FVC as the outcome variable and standardised rank Baseline FVC as a covariate.

Results: Some 171 were randomised to pirfenidone and 173 to placebo. 81% in the pirfenidone group and 85% in the placebo group completed the study (see Table 10 in Attachment 2). Most patients were White (98.8% and 98.8%), male (71.9%, 71.7%), and ≥ 65 years of age (59.0%, 64.8%).

The primary efficacy variable was the mean change from Baseline in percentage predicted FVC (shown below in Figure 2).

Figure 2: Mean Change from Baseline FVC in Study PIPF-006 from 0 to 72 weeks in pirfenidone (2,403 mg/day) versus placebo group
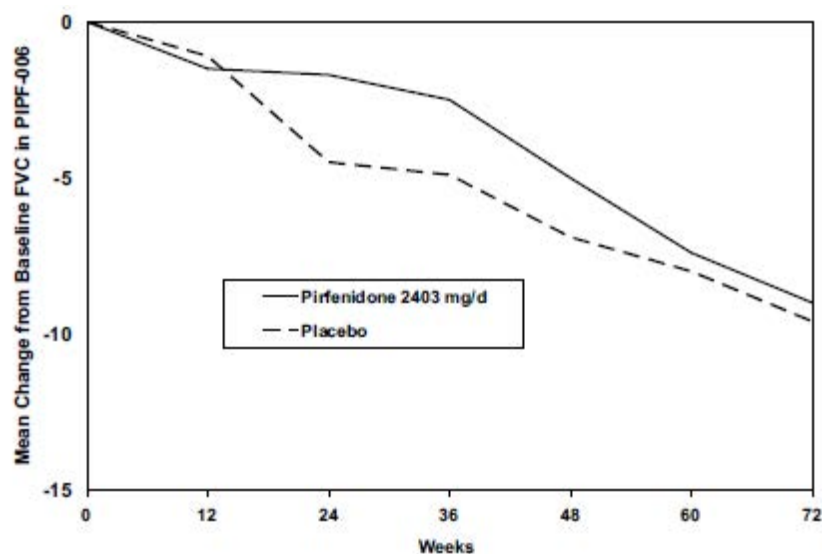
This showed no significant difference between groups at Week 72. Between Week 12 and Week 48 there was a difference between groups for this outcome variable.

Other efficacy results reported by the evaluator were that, 'for the categorical assessment of change in % predicted FVC, a lower proportion of patients receiving pirfenidone had a moderate or severe decline (specifically, a decline of ≥ 10%) in percent predicted FVC at week 72 (22.8%, 39 out of 171 pirfenidone versus 26.6%, 46 out of 173 placebo) and a slightly higher proportion had mild or moderate improvement (25.8%; 44 out of 171 versus 22.0%, 38 out of 173), but differences were not statistically significant.

There were similar PFS rates (68.2%, 116 out of 170 versus 65.1%, 112 out of 172 for pirfenidone or placebo respectively).

Study PIPF-016

Study PIPF-016 was submitted to the FDA. It was a randomised, double blind, placebo controlled, multinational study to evaluate efficacy and safety of pirfenidone in patients with IPF over 52 weeks. The evaluator mentions the inclusion criteria in the evaluation and states that 'the eligibility criteria included patients with a greater risk of disease progression compared to PIPF-004 and PIPF-006'. This included lower percent predicted carbon monoxide diffusing capacity of the lung (DL_{co}), higher FEV_1/FVC ratio, and longer time since IPF diagnosis.

IPF patients were randomised 1: 1 to either pirfenidone 2,403 mg /day (n = 278) or matching placebo (n = 277) treatment for 52 weeks, with dose escalation over the first 14 days.

The primary efficacy outcome was the change in % predicted FVC from Baseline to Week 52.

The secondary efficacy endpoints were change in 6MWT distance from Baseline to Week 52; progression free survival defined as time to first occurrence of any of the following: death, confirmed ≥ 10% absolute decline from Baseline in % predicted FVC, or confirmed ≥ 50 m decline from Baseline in 6MWT distance. These were different to the secondary endpoints of the previous studies. An additional endpoint was mortality including all-cause and treatment emergent IPF related mortality.

Statistical testing methodology was discussed and is acceptable.

Some 278 patients were randomised to pirfenidone and 277 to placebo. 80% in the pirfenidone group and 85.9% in the placebo group completed the study. For subject disposition see Figure 5 in Attachment 2.

Baseline demographic characteristics were comparable between the treatment groups; most study patients were White (91.2%), male (78.4%), and ≥ 65 years of age (71.0%; overall mean 68.1 years). Prior medications were generally comparable; systemic corticosteroids were used by a total of 2.2% and 0.7% of patients in pirfenidone and placebo groups, respectively.

The primary efficacy analysis of the change in the percent predicted FVC from Baseline at Week 52 demonstrated a statistically significant treatment effect of pirfenidone compared with placebo (p < 0.000001, rank ANCOVA).

Table 13. Change in percent predicted FVC between Baseline and Week 52 in pirfenidone versus placebo treated cohorts

| Change from Baseline at Week 52[a] | Number of Patients, n (%) | | p-value[a] |
	Pirfenidone 2403 mg/d (N = 278)	Placebo (N = 277)	
Decline of ≥10% or death	46 (16.5)	88 (31.8)	<0.000001
Decline of <10% to 0%	169 (60.8)	162 (58.5)	
No decline (change in percent predicted FVC >0%)	63 (22.7)	27 (9.7)	

[a] p-value by rank ANCOVA
FVC = forced vital capacity

Change from Baseline to week 52 in 6MWT distance: The proportion of patients having an absolute decline ≥ 50m at Week 52 was 25.9% pirfenidone versus 35.7% placebo.e.

Progression free survival: Pirfenidone was associated with significant risk reduction; HR 0.57, 95% CI 0.43 to 0.77.

Mortality: A smaller proportion of patients died in the pirfenidone group (4.0%) than the placebo group (7.2%). Analyses suggested a non-significant reduced risk of all-cause mortality through the Week 52 time point for pirfenidone compared with placebo, HR 0.55; 95% CI, 0.26 to 1.15; p = 0.1045, log rank test. The clinical evaluator mentions that the study was not powered for this or other mortality endpoints.

Overall efficacy conclusions: the clinical evaluator mentioned that the primary efficacy endpoint used in these studies was relevant to the indication. However, the absolute treatment effect observed was small. The primary efficacy variable was statistically significant favouring pirfenidone in Studies PIPF-004 and PIPF-016. This was not statistically significant in Study PIPF-006 and may have partly been due to the 'placebo group in PIPF-006 demonstrated a smaller decline in % predicted FVC than placebo group in PIPF-004, consistent with variability in disease progression.'

The clinical evaluator mentioned that, 'due to apparent heterogeneity of the IPF study population in the earlier studies, changes in study population selection in PIPF-016 were directed towards increasing the proportion at risk of progression from IPF (increased duration of diagnosis, reduction in lower limit of DL_{CO}), and reducing the proportion of subjects with significant co-existing COPD (FEV_1/FVC ratio < 0.8 after administration of bronchodilator at screening, confirmed by central review) while enlarging the sample size'. This study showed statistically significant superiority of the active treatment versus placebo in relation to the primary efficacy endpoint.

Overall, efficacy was demonstrated in the studies submitted.

Safety

The clinical evaluator tabulated the numbers involved in the Phase I, Phase II and Phase III studies.

The 'randomised patient subset' was the 2,403 mg/day pirfenidone (n = 623) and the placebo groups (n = 624) from PIPF-004, PIPF-006, and PIPF-016. Overall the demographics across treatment groups were well balanced. Most of the information below focuses on information from this subset.

The 'pirfenidone patient subset' additionally included patients from PIPF-002 and PIPF-012, and those treated with pirfenidone 1,197 mg/day in PIPF-004 (total patients, n = 1,067; patients treated with the maximum dose of 2,403 mg/day of pirfenidone, n = 980).

Long term exposure in clinical studies included 172 patients treated for at least five years.

All AEs in the randomised subset: The most frequently reported events with incidence greater for pirfenidone compared to placebo were GI disorders (pirfenidone 72% versus placebo 52%) for example, nausea (36% versus 15%), diarrhoea (26% versus 20%), dyspepsia (18% versus 7%) and vomiting (13% versus 6%). This was followed by skin disorders (41% versus 15%), rash (30% versus 10%), photosensitivity (9% versus 1%), and pruritus (8% versus 5%). In other SOCs differences were seen in fatigue (26% versus 19%), dizziness (18% versus 11%), anorexia (13% versus 5%), insomnia (10% versus 7%), decreased body weight (10% versus 5%) and hot flush (4% versus 2%).

The most commonly reported ADRs in the randomised patient subset (based on investigator assessment) in patients treated with pirfenidone compared to placebo respectively, were: nausea (32.4% versus 12.2%), rash (26.2% versus 7.7%), diarrhoea (18.8% versus 14.4%), fatigue (18.5% versus 10.4%), dyspepsia (16.1% versus 5.0%), anorexia (11.4% versus 3.5%), headache (10.1% versus 7.7%), and photosensitivity reaction (9.3% versus 1.1%).

Deaths: A total of 71 patients died within 28 days of last dose of study treatment, lower in the pirfenidone than placebo group (4.3%, 27 patients versus 7.1%, 44 patients). IPF was the most common cause of death (10 pirfenidone, 1.6% versus 21 placebo, 3.4%).

Treatment emergent SAEs were reported in approximately 28% in each group. The three most frequently reported SAEs (IPF, pneumonia, and respiratory failure) were reported in a smaller proportion of pirfenidone treated patients compared with placebo treated patients. SAEs that were reported more frequently in the pirfenidone 2,403 mg/day group compared to placebo included the following: coronary artery disease (n =7 (1.1%) versus n = 3 (0.5%)) and angina pectoris (n = 6 (1.0%) and n = 2 (0.3%)).

Adverse Events of special interest:

Liver toxicity: the clinical evaluator states that in the randomised patient subset 9.5% pirfenidone patients reported hepatic TEAEs versus 4.3% for placebo. There were 6 pirfenidone patients with hepatic treatment emergent SAEs versus 1 placebo patient.

The US FDA report states that: '*Fifteen pirfenidone treated patients had a maximum post-Baseline ALT or AST elevation of 3 to 5 x ULN. Of note, 12 of these patients remained on pirfenidone until study completion, with 7 on a full dose, and 5 on a reduced dose. In the overall safety database, ALT and AST elevations were infrequent, but occurred in a larger proportion of patients on pirfenidone than on placebo. For example, AST elevations 3 to 5 times of normal were reported in 1.3% and 0.5% in pirfenidone and placebo treated patients, respectively; and ALT elevations 3 to 5 times of normal were reported in 1.9% and 0.3% in pirfenidone and placebo treated patients, respectively. Elevation of AST or ALT along with elevation of bilirubin was reported in one patient who had Gilbert's disease as described above*'.

The clinical evaluator requested that the 'Precautionary Statements' which are contained in the US monograph be included in the Australian PI. The sponsor has complied.

Photosensitivity reaction was reported for 9.3% of pirfenidone patients and 1.1% of placebo patients in the randomised patient subset, most within the initial 6 months. The PI notes that patients must be protected from sunlight.

The most common GI adverse events reported more frequently in pirfenidone patients when compared with placebo included nausea (36% versus 16%), diarrhoea (26% versus 20%), dyspepsia (19% versus 7%), vomiting (13% versus 6.3%), and gastro-oesophageal reflux disease (GORD (11% versus 7%).

The evaluator concludes that the overall safety profile is acceptable. The evaluator also states that the occurrence of adverse events may be dealt with by dose titration. Some serious events require prompt assessment. PI recommendations sought to address these issues have been addressed satisfactorily by the sponsor.

Clinical evaluator's questions

The clinical evaluator recommended several PI amendments that were adopted by the sponsor.

The clinical evaluator also requested clarifications relating to some aspects of efficacy and safety, of note, the discrepancy between the EMA approval of the indication of '*mild to moderate IPF*' and the proposed indication in Australia of '*treatment of IPF*'. The sponsor's response states that this is consistent with the data provided to the FDA (inclusion of an additional Study PIPF-016) where patients with greater likelihood of disease progression were included. This was considered acceptable by the clinical evaluator.

Overall benefits

There was an improvement in relation to the primary efficacy endpoint, reduction in the decline of percent predicted FVC; there was also a suggestion of reduction in mortality in the pooled clinical studies.

Overall risks

Drug interactions are mentioned; other events (CNS, GI and hepatic events) were well characterised.

Overall risk-benefit assessment

The clinical evaluator deemed that overall the risk-benefit balance was favourable.

Risk management plan

RMP evaluation

Overall, there are no significant outstanding issues. The sponsor is requested to provide the draft education materials to TGA before approval/launch.

This submission was considered by ACSOM at a recent meeting. The draft minutes state that in relation to monitoring and management of photosensitivity reaction and rashes and in relation to hepatic related events that strategies to be implemented in the EU, including mail outs to healthcare practitioners is also appropriate to undertake in Australia.

Risk-benefit analysis

Issues

There is an outstanding concern identified in the quality evaluation regarding the proposed limit of impurity D in the drug substance, NMT than 0.05% that has not been qualified (the specified impurity is genotoxic (clastogenic) and closely related to benzene, a known human carcinogen).[3] On the basis of the toxicological advice, the permitted daily exposure (PDE) limit for the specified impurity in pirfenidone drug substance is 133 µg/day at the maximum recommended drug dose of 2,403 mg/day. This corresponds to a maximum limit of 0.0055% of the specified impurity in the drug substance. Clearly, the proposed limit exceeds the permitted daily dose. The sponsor should reduce the limit to acceptable levels.

This issue has not been identified in the EU and FDA reports regarding the same product.

In view of the significant morbidity associated with IPF and the fact that the median survival after diagnosis is 2 to 5 years, the Delegate is of the opinion that this formulation of pirfenidone can be registered at the present time. However, the sponsor should reduce the impurity limit to safe levels and this should be a condition of registration.

Delegate's considerations

The Delegate agrees with the clinical evaluator that the risk-benefit profile is satisfactory to warrant the registration of pirfenidone (as Esbriet) at the specified doses for IPF.

Proposed action

The Delegate had no reason to say, at this time, that the application for Esbriet should not be approved for registration.

Request for ACPM advice

The committee was requested by the Delegate to provide advice on the following specific issues:

1. Does the Committee agree with the Delegate that the risk benefit profile is acceptable given that there is a toxicological concern expressed on the limit set for the specified impurity?

2. Does the Committee agree that in relation to monitoring and management of photosensitivity reactions and rashes and in relation to hepatic related events, that strategies to be implemented in the EU including mail outs to healthcare practitioners, is also appropriate to undertake in Australia?

Response from sponsor to issues raised by the Delegate

Roche (the sponsor) agrees with the TGA's assessment that the risk benefit profile of Esbriet is satisfactory to warrant the registration at the specified doses for idiopathic pulmonary fibrosis.

Roche notes the Delegate's Summary of Issues and requests for ACPM advice in relation to:

1. *Does the Committee agree with the Delegate that the risk benefit profile is acceptable given that there is a toxicological concern expressed on the limit set for the specified impurity [information redacted]*

2. Does the Committee agree that in relation to monitoring and management of photosensitivity reactions and rashes and in relation to hepatic related events; that strategies to be implemented in the EU including mail outs to healthcare practitioners, is also appropriate to undertake in Australia?

The sponsors' responses to the Delegate's request for ACPM advice are included below:

1. Benefit Risk profile and the specified impurity[3]

    a. Summary benefit risk profile

    b. Overview of non-clinical evaluations related to the specified impurity

    c. Review of potential clastogenic cancer-related effects of the specified impurity

2. Monitoring and management of photosensitivity reactions and rashes and in relation to hepatic related events

1. ***Benefit Risk profile and the specified impurity[3]***

    a. Summary benefit risk profile

IPF is a fatal and devastating rare disease of unknown aetiology that represents an urgent unmet medical need. IPF is characterized by progressively decreasing lung volume, worsening dyspnoea, and diminishing exercise capacity and, is recognized as a distinct form of chronic fibrosing interstitial pneumonia that occurs primarily in older adults, limited to the lungs, and is defined by a radiologic and histopathologic pattern of usual interstitial pneumonia.[34] IPF is irreversible and ultimately fatal, with patients suffering from a relentless and debilitating loss of lung function that ultimately culminates in death, with an estimated median survival after diagnosis of only 2.5 to 5 years.[35][36][37][38][39][40][41][42][43]

Esbriet has been approved for the treatment of patients with IPF in the EU, USA, Canada, and Switzerland. The data included in the application provide compelling evidence that the clinical benefits of Esbriet outweigh the risks in patients with IPF. Additional, substantiating, information is provided below:

Pirfenidone is an orally active, small molecule that exerts both anti-fibrotic and anti-inflammatory properties as demonstrated in more than 40 animal models and in vitro systems.[44]

---

[34] Raghu G 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.

[35] Bjoraker J et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;157:199–203.

[36] Mapel D et al. Idiopathic pulmonary fibrosis: survival in population based and hospital based cohorts. *Thorax* 1998;53:469–476.

[37] Douglas W et al. Idiopathic pulmonary fibrosis: impact of oxygen and colchicine, prednisone, or no therapy on survival. *Am J Respir Crit Care Med* 2001; 161:1172–1178.

[38] Nicholson A et al. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 2000;162:2213–2217.

[39] King T Jr et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001;164:1171-1181.

[40] Collard H et al. Changes in clinical and physiological variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;168:538– 542.

[41] Rudd R et al. for the Fibrosing Alveolitis Subcommittee of the Research Committee of the British Thoracic Society. 2007. British Thoracic Society Study on cryptogenic fibrosing alveolitis: response to treatment and survival. *Thorax* 2007;62:62–66.

[42] Fernández Pérez E et al. Incidence, prevalence, and clinical course ofidiopathic pulmonary fibrosis. A population- based study. *Chest* 2010;137:129–137.

[43] Kim J et al. Clinical predictors of survival in idiopathic pulmonary fibrosis. *Tuberc Respir Dis* 2012;73:162-168.

[44] Du Bois R. 2 Strategies or treating idiopathic pulmonary fibrosis. *Nat Rev Drug Discov* 2010;9:129–140

The clinical development program of Esbriet in IPF spans more than two decades including multiple studies to assess the safety and clinical pharmacology of Esbriet in healthy volunteers, patients with IPF, and in relevant special populations. The efficacy and safety of Esbriet in patients with IPF has been studied in three adequate and well controlled, randomised, double blind, placebo controlled Phase III studies comparing pirfenidone 2,403 mg/day and placebo in a total of 1,247 patients with IPF; studies PIPF-004 and PIPF-006 and a confirmatory Phase III Study (PIPF-016). The totality of the data indicates that Esbriet treatment alters the natural history of this uniformly fatal disease (see Figure 3 below).

Figure 3: Overview of efficacy endpoints at Month 12 in pooled Studies PIPF-016, PIPF-004, and PIPF-006 (All Randomized Patients)
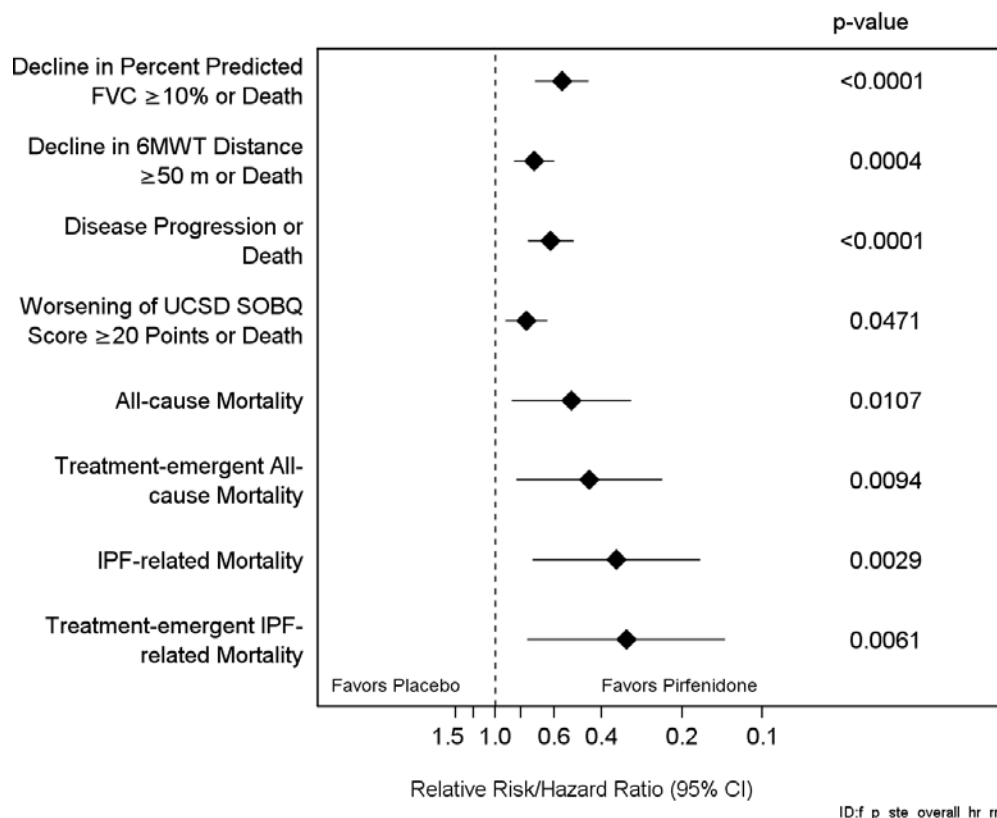
Note: 95% CI for relative risks (percent predicted FVC, 6MWT distance and UCSD SOBQ) is estimated with the log normal approximation.

A total of 1,098 persons in the clinical studies database have received Esbriet dose of 2,403 mg/day or greater, and the total clinical exposure to Esbriet spanning Phase II and Phase III studies equals 2,876 patient exposure years. These data, combined with an extensive worldwide post marketing experience in excess of 13,000 patient years of treatment throughout Europe, Japan, and Canada, comprise a robust safety database for this indication.

The totality of the data demonstrates a favourable safety profile of Esbriet in patients in the context of a progressive and fatal disease. Reported AEs are primarily related to tolerability rather than morbidity. Use of measures to improve tolerance (such as dose escalation in the first 2 weeks, dosing with food, protection from sun exposure), routine monitoring of liver tests, as well as prompt identification and symptomatic management of adverse reactions, enable ongoing use of Esbriet in most patients with IPF.

In conclusion, IPF is a fatal disease characterized by a progressive and debilitating loss of lung function and death. The totality of the data evaluating Esbriet for the treatment of IPF

demonstrates that Esbriet reduces decline in lung function and in exercise capacity, prolongs progression free survival, and most importantly, reduces the risk of all-cause and IPF related mortality. Treatment with Esbriet thus provides clear and clinically meaningful benefit to patients with IPF. The extensive experience in the combined clinical studies and post marketing setting, demonstrates that Esbriet is generally safe and well tolerated within the proposed labelling and that the projected benefits of this treatment outweigh known and theoretical risks for patients with IPF.

b. ***Impurity specified impurity***

Four process-related impurities have been identified in the pirfenidone drug substance and are proposed to be controlled at a limit of NMT 0.05%. These limits have been accepted by regulatory agencies globally where Esbriet is approved including, the USA, EU, Canada and Switzerland. In addition the European Pharmacopeia monograph for pirfenidone, effective January 2016, will also list the 4 impurities with a limit of NMT 0.05%.[45]

The TGA has raised concerns regarding the specified impurity and its genotoxic (clastogenic) potential and the proposed specification of NMT 0.05% yielding a daily dose of 1200 µg/day.

i. *Overview of Nonclinical evaluations related to the specified impurity*

An assessment to evaluate the mutagenicity and clastogenicity potential of specified impurity including 2 complementary in silico programs, a review of the available safety assessment literature and an overall review of the data by Roche's genotoxic impurity expert was undertaken.

Based on the weight of evidence, the genotoxic expert concluded that none of the multiple studies examining bacterial gene mutation reported in the literature suggested that specified impurity had mutagenic potential. Positive results for clastogenicity were observed only at high, cytotoxic doses in two assays: (1) specified impurity was weakly positive in a sister chromatid exchange assay in Chinese hamster ovary (CHO) W-B1 cells in the absence of metabolic activation at the highest dose tested (500 µg/mL) and (2) a dose of 125 mg/kg (2 x 62.5 mg/kg) in mice resulted in a positive micronucleus results in polychromatic erythrocytes.[46][47] This positive result is contradicted by more recently published data. A negative result was obtained in peripheral blood at significantly greater doses up to 1,200 mg/kg or 600 mg/kg.[48] In a rat liver micronucleus assay specified impurity was equivocally positive when administered at a high, partially lethal dose (1,200 mg/kg) but not at a non-lethal dose (600 mg/kg). These data call into question the positive result reported and may suggest that any positive result may not be generalizable to all species. The weight of evidence, including more recently published literature, supports the assertion that specified impurity is not mutagenic or clastogenic at concentrations where cytotoxic effects are not observed.

---

[45] European Pharmacopeia Monograph: Pirfenidone EP-2865E.

[46] Galloway S et al.Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. *Environ Mol Mutagen* 1987; 10:1-175.

[47] Mohtashamipur, E et al. The bone marrow clastogenicity of eight halogenated benzenes in male NMRI mice. *Mutagenesis* 1987; 2 :111-113.

[48] Takasawa H et al. Evaluation of a liver micronucleus assay in young rats (IV): a study using a double-dosing/single-sampling method by the Collaborative Study Group for the Micronucleus Test (CSGMT)/Japanese Environmental Mutagen Society (JEMS)-Mammalian Mutagenicity Study Group (MMS). *Mutat. Res*. 2010;698: 24-29.

ii. *Review of potential clastogenic cancer related effects of specified impurity*

Clastogenic effects may involve germ line and somatic cells.[49] Regarding potential effect on germ line cells:

- The RMP and the proposed PI both describe fertility effects identified in preclinical studies and state that as '*a precautionary measure, it is preferable to avoid the use of Esbriet during pregnancy*.' The sponsor believes that this labelling information would potentially mitigate any pregnancy related risks from clastogenic effects on germ lines.

- There is currently no data to assess clastogenic effects on germ lines as there is no pregnancy outcome data in the Roche safety database for pirfenidone exposed patients.

The other type of the clinical manifestation of clastogenic effects would involve somatic cells. Should this to be the case, one would hypothetically observe an increase rate of neoplasia in IPF patients exposed to specified impurity via Esbriet use, relative to rates in unexposed IPF patients and general population.[50]

There are however important considerations inherent to the natural history of IPF, the indication for Esbriet, that would preclude the possibility of observing such rates; the latency of tumorigenesis and the feasibility of a cancer diagnosis related to exposed to specified impurity via Esbriet use.

As noted above, IPF is a devastating, older age related lung disease of unknown cause that has few treatment options and a poor median survival time from 2.5 to 5 years from the time of diagnosis, which is worse than many cancers.[51][52][53][54] In addition, it is well known that both the final, formal diagnosis of IPF and the start of treatment with Esbriet are often delayed.

The clinical manifestation of any potential clastogenic effect takes an extended period of time. A cell sustaining a chromosomal change that triggers a cancerous process would need to undergo many years of cell doubling before becoming clinically detectable. There is published evidence in the literature that tumour development almost always involves a long delay between the initial causal event, exposure dose and duration, and the onset of disease. One example of latency suggest that prostatic carcinogenesis starts in the second to third decade of life and may require over 50 years for progression to pathologically detectable metastatic disease.[55] In fact, for most solid human tumours, there is a 20 year interval from carcinogen exposure to clinical detection.[56] It has been observed that '*villous tumour, proven histologically, will remain benign for up to twenty years without becoming malignant'*.[57] Studies calculating the growth of lung tumours based on mathematical models suggest that it takes 10 to 15 years from the appearance of the first cancer cell to the possibility of detecting a non-small cell lung cancer by conventional chest

---

49 Rose, J. *Environmental Toxicology: Current Developments*, 1998; p. 64.

50 Friedrich V. ch. Mutation: Somatic Mutation, Cancer, and Aging *Human Genetics,* 1997; pg:43 -456.

51 American Thoracic Society Documents: An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management; *Am J Respir Crit Care Med* 2011; Vol 183. pp 788–824

52 Talmadge E et al. Idiopathic pulmonary fibrosis; *Lancet* 2011; 378:9807 pg. 1949–61

53 Srikumar M et al. Outcome of patients with idiopathic pulmonary fibrosis (IPF) ventilated in intensive care unit; *Respiratory Medicine* 2008; 102: 1355–59

54 Dong K et al. Classification and Natural History of the Idiopathic Interstitial Pneumonias; *Proc Am Thorac Soc* 2006; 3: 285–292.

55 Berges R et al. Implication of cell kinetic changes during the progression of human prostatic cancer ; *Clinical Cancer*, 1995

56 Loeb L et al. Multiple mutations and cancer; *PNAS.* 2003; 100:3 pg. 776–781

57 Morson B et al. The Polyp cancer Sequence in the *Large Bowel;Proc R Soc Med.* 1974; 67: 451–457

radiograph.[58] An example reflective of the effect of dose and duration of exposure is that the incidence of lung cancer rises steeply 10 to 20 years of heavy smoking.[59]

In the absence of pirfenidone pregnancy safety outcome data to assess clinical manifestation of clastogenic effects on germ-lines, the sponsor assessed the clinical manifestation of potential clastogenic effects in somatic cells. The potential clinical manifestation of such potential clastogenic effects in somatic cells would potentially be manifested if there were an increase in rates of neoplasm in patients receiving Esbriet.

Roche has conducted a review of potential clastogenic cancer-related effects of specified impurity, which included a cumulative review of all pirfenidone cases within the Roche safety database, and events included in the MedDRA system organ Class (SOC) Neoplasms benign, malignant and unspecified (including cysts and polyps).

Cumulative review of Neoplasm cases in the Esbriet Safety Database

A cumulative review of pirfenidone cases in the Roche safety database was performed to identify any event with the MedDRA SOC of Neoplasms benign, malignant and unspecified (including cysts and polyps). In all, 359 cases were identified. Of these 359 cases, 1 was Literature Non- Interventional Study/Program, 77 were spontaneous, 156 were solicited, and 125 were clinical reports.

The cumulative patient-years of exposure to pirfenidone, as of 27 February 2015 (the Data Lock Point (DLP) of the most recent PSUR), was 20,368. Neoplasm events in patients exposed to pirfenidone, were reported at a rate consistent with an incidence of 1,762.6/100,000 patient years (359/20,368).

The sponsor is aware of two reasons why this value of 1,762.6 per 100,000 patient-years is possibly over-reporting the events for this SOC:

- Approximately 43% of identified cases, reported with this SOC, were from solicited reports. Solicited cases have been described in the scientific literature as having an increased reporting rate when compared to spontaneous reports.[60][61] This would increase the numerator in the incidence calculation.

- The cumulative patient years of exposure to pirfenidone that was used for the dominator in the incidence calculation will be smaller than what would be available for the DLP used in this cumulative review.

Cancer occurs at a higher incidence in the older patient population. About one out of 10 patients with IPF also develops lung cancer.[62] The reported incidence of all neoplasms combined in the safety database (1,762.6 per 100,000) is comparable to the incidence of 2085.3 to 2255.1 per 100,000 that is seen in elderly patients in the general population and smaller than reported for IPF patients unexposed to pirfenidone of 3,730 per 100,00 (373 per 10,000 patient years).[39,40,63]

Pirfenidone's potential manifestation of chromosomal damage (as manifested by a potential increase in the reporting of neoplasms above what would be expected in this patient population) has not been identified in this analysis of the safety data that is based on 20,368 cumulative patient years of exposure to Esbriet.

---

[58] Salomaa E et al. Delays in the Diagnosis and Treatment of Lung Cancer; Clinical Investigations: lung cancer *Chest.* 2005; 128,4: pg 2282-2288

[59] McCance et al. Pathophysiology The Biologic Basis for Disease in Adults and Children, Mosley, Third Edition
[60] Wernicke et al. Detecting treatment emergent adverse events in clinical trials: a comparison of spontaneously reported and solicited collection methods*. Drug Saf.* 2005;28:1057-1063.

[61] Hazell L et al. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf.* 2006; 29: 385-396.
[62] Katerina M et al. Idiopathic pulmonary fibrosis and lung cancer: a clinical and pathogenesis update. *Curr Opin Pulm Med* 2015; 21:626–633.

[63] Le Jeune A et al. The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Respiratory Medicine* 2007; 101: 2534–2540

Conclusion to issues related to specified impurity content

In the context of (1) a median IPF survival of 2.5 to 5 years, (2) the long latency of tumorigenesis process and the small dose and duration of specified impurity exposure via Esbriet, the likelihood of identifying clinically detectable, clastogenic related cancers due to specified impurity exposure within the lifetime of IPF patients would be remote. The lifespan on a person diagnosed with IPF is on average much shorter than the hypothesized latency of a tumour. Exposure to Esbriet would likely be even shorter. This risk-benefit determination in this instance is for a disease with poor median survival time that ranges from 2.5 to 5 years from the time of diagnosis. This survival time is worse than that for many cancers.

The overall body of evidence from the studies of Esbriet, in the setting of this irreversible and fatal orphan disease that represents an urgent unmet medical need, clearly establishes a favourable therapeutic benefit-risk profile that strongly supports the use of Esbriet for the treatment of patients with IPF. We therefore strongly agree with the TGA, that this formulation of pirfenidone can be registered at this time, pending the resolution of the impurity level as a condition of registration if needed.

2. *Does the Committee agree that in relation to monitoring and management of photosensitivity reactions and rashes and in relation to hepatic related events that strategies to be implemented in the EU including mail-outs to healthcare practitioners, is also appropriate to undertake in Australia?*

As agreed in earlier responses, Roche will implement equivalent risk minimisation activities in Australia as those implemented in Europe in relation to photosensitivity reactions and rashes and hepatic related events, for instance provide a DHCPL at launch.

Advisory Committee Considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Esbriet capsule containing 267 mg of pirfenidone to have an overall positive benefit–risk profile for the indication:

> *Esbriet is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).*

In making this recommendation the ACPM noted the evidence presented supported modest efficacy.

Proposed PI/ CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- statements in the 'Precautions' section of the PI and reflected in the relevant sections of the CMI to reference the need for monitoring of the potential adverse events should be highlighted, particularly of rashes and photosensitivity and hepatic disorders.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the committee agree with the Delegate that the risk-benefit profile is acceptable given that there is a toxicological concern expressed on the limit set for the specified impurity [information redacted]?*

The ACPM noted the proposed limit of the specified impurity, exceeds the permitted daily dose. However, in view of the significant morbidity associated with IPF; the clastogenic effect is likely to take many decades to become clinically apparent while average length of

survival in IPF is 2.5 to 5 years. The ACPM was of the view that the benefit-risk balance is still favourable.

The ACPM advised that the sponsor should reduce the impurity limit to safer levels and this could be a condition of registration.

2. *Does the committee agree that in relation to monitoring and management of photosensitivity reactions and rashes and in relation to hepatic related events, that the strategies to be implemented in the EU including mail outs to healthcare practitioners, is also appropriate to undertake in Australia?*

The ACPM noted that in the randomised patient subset gastrointestinal disorders were the most common AEs followed by skin disorders, including photosensitivity reaction which was reported for 9.3% of pirfenidone patients versus 1.1% of the placebo group. There were 6 pirfenidone patients with serious hepatic TEAEs compared to 1 placebo patient.

As this is a rare disease, which should be managed by respiratory physicians, any educational strategies should be targeted at those who will be the most likely prescribers. Australian patients should be educated, especially concerning the photosensitivity. Monitoring of these potential adverse events should be highlighted both in educational literature and the PI.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Esbriet (pirfenidone) 267 mg hard capsules for oral administration indicated for:

> *Esbriet is indicated for the treatment of idiopathic pulmonary fibrosis (IPF)*

Specific conditions of registration applying to these goods

The Esbriet (pirfenidone) EU Risk Management Plan (RMP), Version 7.2, dated 27 July 2015 (data locked point (DLP) 27 February 2015) and ASA Version 1.1, dated 30 October 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Esbriet at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration