NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Esbriet 267 mg hard capsule*
Esbriet 267 mg film coated tablets
Esbriet 534 mg film coated tablets
Esbriet 801 mg film coated tablets

*This product is no longer supplied.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 267 mg pirfenidone
Each film-coated tablet contains 267 mg pirfenidone.
Each film-coated tablet contains 534 mg pirfenidone.
Each film-coated tablet contains 801 mg pirfenidone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Two piece capsules with a white to off-white opaque body and white to off-white opaque cap imprinted with 'PFD 267 mg" in brown ink and containing white to pale yellow powder.

Film-coated tablet.
Esbriet 267 mg film-coated tablets are yellow, oval, approximately 1.3 x 0.6. cm biconvex film-coated tablets, debossed with "PFD".
Esbriet 534 mg film-coated tablets are orange, oval, approximately 1.6 x 0.8 cm biconvex film-coated tablets, debossed with "PFD".
Esbriet 801 mg film-coated tablets are brown, oval, approximately 2 x 0.9 cm biconvex film-coated tablets, debossed with "PFD".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Dose

Adults
The recommended daily dose of Esbriet for patients with IPF is 801mg three times a day with food, for a total of 2403 mg/day.

Upon initiating treatment, the dose should be titrated to the recommended daily dose of 2403 mg/day over a 14 day period as follows:

- Days 1 to 7: a dose of 267 mg administered three times a day (801 mg/day)
- Days 8 to 14: a dose of 534 mg administered three times a day (1602 mg/day)
- Day 15 a dose of 801 mg administered three times a day (2403 mg/day)

Doses above 2403 mg/day are not recommended for any patient (see section 4.9).

Missed doses
Patients who miss 14 consecutive days or more of Esbriet treatment should re-initiate therapy by undergoing the initial 2 week titration regimen up to the recommended daily dose.
For treatment interruption of less than 14 consecutive days, the dose can be resumed at the previous recommended daily dose without titration.

Dose Adjustments and Other Considerations

Gastrointestinal events
In patients who experience intolerance to therapy due to gastrointestinal side effects, patients should be reminded to take Esbriet with food. If symptoms persist the dose of Esbriet may be reduced to 267 mg – 534 mg taken two to three times a day with food with re-escalation to the recommended daily dose as tolerated. If symptoms continue, patients may be instructed to interrupt treatment for one to two weeks to allow symptoms to resolve.

Photosensitivity reaction or rash
Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded to use a sunblock daily and to avoid exposure to the sun (see section 4.4). The dose of Esbriet may be reduced to 801 mg each day (267 mg three times daily). If the rash persists after 7 days, Esbriet should be discontinued for 15 days, with re escalation to the recommended daily dose in the same manner as the dose escalation period.

Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice (see section 4.4). Once the rash has resolved, Esbriet may be reintroduced and re-escalated up to the recommended daily dose at the discretion of the physician.

Hepatic function
If a patient exhibits an aminotransferase elevation >3 to < 5 × ULN without bilirubin elevation after starting Esbriet therapy, confounding medicinal products should be discontinued, other causes should be excluded, and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered. If clinically appropriate the dose of Esbriet should be reduced or interrupted. Once liver function tests are within normal limits Esbriet may be re-escalated to the recommended daily dose if tolerated.

If a patient exhibits an aminotransferase elevation to >3 to < 5 × ULN accompanied by symptoms or hyperbilirubinemia, Esbriet should be discontinued and the patient should not be rechallenged.

If a patient exhibits an aminotransferase elevation to ≥5 × ULN, Esbriet should be discontinued and the patient should not be rechallenged.

Special Populations

Elderly
No dose adjustment is necessary in patients 65 years and older (see section 5.2).

Hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment (i.e., Child-Pugh Class A and B). However, since plasma levels of pirfenidone may be increased in some individuals with mild to moderate hepatic impairment, caution should be used with Esbriet treatment in this population. Patients should be monitored closely for signs of toxicity especially if concomitantly taking a known CYP1A2 inhibitor. Esbriet has not been studied and is not recommended in patients with severe hepatic impairment or end stage liver disease. It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations (see section 4.3, 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary in patients with mild renal impairment. Esbriet should be used with caution in patients with moderate renal impairment (CrCl 30-50mL/min) to severe (CrCl <30mL/min) renal impairment due to lack of information relating to the metabolite (see section 5.2). Esbriet has not been studied and is not recommended in patients with end-stage renal disease requiring dialysis (see section 4.3 and 5.2).

Method of Administration
Esbriet is for oral use. The capsules are to be swallowed whole with water and taken with food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Concomitant use of fluvoxamine (see section 4.5)
- History of angioedema with pirfenidone (see section 4.4)

4.4 Special warnings and precautions for use

Hepatic Function
Drug-Induced Liver Injury (DILI) in the form of transient and clinically silent elevations in transaminases, has been commonly reported in patients treated with Esbriet. Uncommonly, these elevations were associated with concomitant bilirubin increases, and serious clinical consequences including isolated cases with fatal outcome have been reported post-marketing.

Liver function tests (ALT, AST and bilirubin) should be performed prior to the initiation of treatment with Esbriet, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter. In addition, liver function tests should be promptly measured in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. In the event of significant elevation of liver aminotransferases or clinical signs and symptoms of liver injury, the dose of Esbriet should be adjusted or treatment discontinued according to the guidelines in section 4.2. For patients with confirmed elevations in ALT, AST or bilirubin during treatment, dose adjustments may be necessary (see section 4.2).

Photosensitivity Reaction and Rash
Exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with Esbriet. Patients should be instructed to use an effective sunblock daily, to wear clothing that protects against sun exposure, and to avoid other medicinal products

known to cause photosensitivity. Patients should be instructed to report symptoms of photosensitivity reaction or rash to their physician. Dose adjustments or temporary treatment discontinuation may be necessary for photosensitivity reaction or rash (see section 4.2).

Angioedema
Reports of angioedema (some serious) such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing have been received in association with use of Esbriet in the post-marketing setting. Therefore, patients who develop signs or symptoms of angioedema following administration of Esbriet should immediately discontinue treatment. Patients with angioedema should be managed according to standard of care. Esbriet should not be used in patients with a history of angioedema due to Esbriet.

Cigarette Smoking and Inducers of CYP1A2
A Phase 1 interaction study evaluated the effect of cigarette smoking (CYP1A2 inducer) on the pharmacokinetics of Esbriet. 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 to Esbriet. Concomitant use of strong inducers of CYP1A2 including smoking should be avoided during Esbriet therapy based on the observed relationship between cigarette smoking and its potential to induce CYP1A2. Patients should be encouraged to discontinue use of strong inducers of CYP1A2 and to stop smoking before and during treatment with pirfenidone.

4.5 Interaction with other medicines and other forms of interaction

Pirfenidone is metabolized primarily via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Fluvoxamine and Inhibitors of CYP1A2
In a Phase 1 study, the co-administration of Esbriet 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.

Esbriet is contraindicated in patients with concomitant use of fluvoxamine (see section 4.3). Fluvoxamine should be discontinued prior to the initiation of Esbriet therapy and avoided during Esbriet therapy due to the reduced clearance of pirfenidone.

In vitro-in vivo extrapolations indicate that strong and selective inhibitors of CYP1A2 have the potential to increase the exposure to pirfenidone by approximately 2 to 4 fold. If concomitant use of Esbriet with a strong and selective inhibitor of CYP1A2 cannot be avoided, the dose of Esbriet should be reduced to 801 mg daily (267 mg three times a day). Patients should be closely monitored for emergence of adverse reactions associated with Esbriet therapy. Discontinue Esbriet if necessary (see section 4.2)

Co-administration of Esbriet and 750 mg of ciprofloxacin (a moderate and selective inhibitor of CYP1A2) increased the exposure to pirfenidone by 81%. If ciprofloxacin at the dose of 750 mg twice daily cannot be avoided, the dose of Esbriet should be reduced to 1602 mg daily (534 mg three times a day). Esbriet should be used with caution when ciprofloxacin is used at a dose of 250 mg or 500 mg once or twice daily.

Esbriet should be used with caution in patients treated with other moderate inhibitors of CYP1A2.

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be avoided during Esbriet treatment.

Inducers of CYP1A2
In the case of moderate inducers of CYP1A2 (e.g., omeprazole), concomitant use may theoretically result in a lowering of pirfenidone plasma levels.

Co-administration of medicinal products that act as potent inducers of both CYP1A2 and the other CYP isoenzymes involved in the metabolism of pirfenidone (e.g., rifampicin) may result in significant lowering of pirfenidone plasma levels. These medicinal products should be avoided whenever possible.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3
There are no data from the use of Esbriet in pregnant women.

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

At high doses (≥1000 mg/kg/day) rats exhibited prolongation of gestation and reduction in fetal viability.

As a precautionary measure, it is preferable to avoid the use of Esbriet during pregnancy.

Breast-feeding

It is unknown whether pirfenidone or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of pirfenidone and/or its metabolites in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk. A risk to the breastfeeding child cannot be excluded.

A decision must be made whether to discontinue breast feeding or to discontinue from Esbriet therapy, taking into account the benefit of breast feeding for the child and the benefit of Esbriet therapy for the mother.

Fertility

No adverse effects on fertility were observed in preclinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Esbriet may cause dizziness and fatigue, which could have a moderate influence on the ability to drive or use machines, therefore patients should exercise caution when driving or operating machinery if they experience those symptoms.

4.8 Undesirable effects

Clinical Trials
The safety of Esbriet has been evaluated in 623 IPF patients from three Phase III clinical studies.

See Table 1 for all ADRs by MedDRA System Organ Class along with their incidence. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1: Adverse Drug Reactions Occurring in Patients Treated with Esbriet in Clinical Trials

ADR (MedDRA)	Esbriet (*n* = 623)	
System Organ Class	All Grades (%)	Frequency Category
Metabolism and Nutrition Disorders		
Weight decreased	10.1%	Very Common
Decreased appetite	20.7%	Very Common
Psychiatric Disorders		
Insomnia	10.4%	Very Common
Nervous System Disorders		
Headache	22.0%	Very Common
Dizziness	18.0%	Very Common
Dysgeusia	5.8%	Common
Gastrointestinal Disorders		
Dyspepsia	18.5%	Very Common
Nausea	36.1%	Very Common
Diarrhoea	25.8%	Very Common
Abdominal pain	6.3%	Common
Vomiting	13.3%	Very Common
Gastro-oesophageal reflux disease	11.1%	Very Common
Hepatobiliary Disorders		
ALT increased	3.2%	Common
AST increased	2.7%	Common
Skin and Subcutaneous Disorders		
Photosensitivity reaction	9.3%	Common
Rash	30.3%	Very Common
Pruritus	7.9%	Common
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	10.0%	Very Common
General Disorders and Administration Site Conditions		

ADR (MedDRA)	Esbriet (*n* = 623)	
System Organ Class	All Grades (%)	Frequency Category
Fatigue	26.0%	Very Common
Asthenia	6.4%	Common

Post-Marketing

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during post-approval use of Esbriet. Because these reactions may be voluntary from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Table 2: Adverse Drug Reactions identified from Post-Marketing Experience

System Organ Class	**Incidence (%)**	**Frequency Category**
Blood and Lymphatic System Disorders		
Agranulocytosis	0.5%[2]	Uncommon[2]
Immune System Disorders		
Angioedema	0.5%[2]	Uncommon[2]
Hepatobiliary Disorders		
Bilirubin increased in combination with increases of ALT and AST	0.2%[1]	Uncommon
Clinically relevant Drug-Induced Liver Injury, including isolated reports with fatal outcome	0.5%[2]	Uncommon

[1] Highest incidence observed during the pivotal clinical trials

[2] The incidence and frequency category for ADRs observed only in the postmarketing setting is defined as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to Esbriet in the pivotal trials.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

There is limited clinical experience with overdose.

In the event of a suspected overdose, supportive medical care should be provided including monitoring of vital signs and close observation of the clinical status of the patient.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, other immunosuppresants, ATC code: L04AX05

Mechanism of Action
The mechanism of action of pirfenidone has not been fully established. However, existing data indicate that pirfenidone exerts both anti-fibrotic and anti-inflammatory properties in a variety of in vitro systems and animal models of pulmonary fibrosis (bleomycin and transplant induced fibrosis).

IPF is a chronic fibrotic and inflammatory pulmonary disease affected by the synthesis and release of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF α) and interleukin 1 beta (IL 1β). Esbriet has been shown to reduce the accumulation of inflammatory cells in response to various stimuli.

Esbriet attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as, transforming growth factor-beta (TGF β) and platelet-derived growth factor (PDGF).

Clinical efficacy and safety
The clinical efficacy of Esbriet has been studied in three multinational, Phase 3, multicenter, randomized, double-blind, placebo-controlled studies in patients with idiopathic pulmonary fibrosis (IPF): PIPF 004, PIPF 006 (CAPACITY) and PIPF-016 (ASCEND).

PIPF 004 and PIPF 006 compared treatment with Esbriet 2403 mg/day to placebo. The studies were nearly identical in design, with few exceptions including an intermediate dose group (1197 mg/day) in PIPF 004. In both studies, treatment was administered three times daily for a minimum of 72 weeks. The primary endpoint in both studies was the change from baseline to Week 72 in percent predicted Forced Vital Capacity (FVC).

In study PIPF 004, the decline in percent predicted FVC from baseline at Week 72 of treatment was significantly reduced in patients receiving Esbriet (N = 174) compared with patients receiving placebo (N = 174; $p = 0.001$, rank ANCOVA). Treatment with Esbriet also significantly reduced the decline in percent predicted FVC from baseline at Weeks 24 ($p = 0.014$), 36 ($p < 0.001$), 48 ($p < 0.001$), and 60 ($p < 0.001$). At Week 72, a decline from baseline in percent predicted FVC of ≥10% (a threshold indicative of the risk of mortality in IPF) was seen in 20% of patients receiving Esbriet compared to 35% receiving placebo (Table 3).

Table3: Categorical Assessment of Change from Baseline to Week 72 in Percent Predicted FVC in Study PIPF-004

	Pirfenidone 2403 mg/day (N = 174)	**Placebo (N = 174)**
Decline of ≥10% or death or lung transplant	35 (20%)	60 (34%)
Decline of less than 10%	97 (56%)	90 (52%)
No decline (FVC change >0%)	42 (24%)	24 (14%)

Although there was no difference between patients receiving Esbriet compared to placebo in change from baseline to Week 72 of distance walked during a six minute walk test (6MWT) by the pre-specified rank ANCOVA, in an ad hoc analysis, 37% of patients receiving Esbriet showed a decline of ≥50 m in 6MWT distance, compared to 47% of patients receiving placebo in PIPF-004.

In study PIPF 006, treatment with Esbriet (N = 171) did not reduce the decline in percent predicted FVC from baseline at Week 72 compared with placebo (N = 173; p = 0.501). However, treatment with Esbriet reduced the decline in percent predicted FVC from baseline at Weeks 24 (p < 0.001), 36 (p = 0.011), and 48 (p = 0.005). At Week 72, a decline in FVC of ≥10% was seen in 23% of patients receiving Esbriet and 27% receiving placebo (Table 4).

Table 4: Categorical Assessment of Change from Baseline to Week 72 in Percent Predicted FVC in Study PIPF-006

	Pirfenidone 2403 mg/day (N = 171)	**Placebo (N = 173)**
Decline of ≥10% or death or lung transplant	39 (23%)	46 (27%)
Decline of less than 10%	88 (52%)	89 (51%)
No decline (FVC change >0%)	44 (26%)	38 (22%)

The decline in 6MWT distance from baseline to Week 72 was significantly reduced compared with placebo (p < 0.001, rank ANCOVA). Additionally, in an ad hoc analysis, 33% of patients receiving Esbriet showed a decline of ≥50 m in 6MWT distance, compared to 47% of patients receiving placebo.

In a pooled analysis of survival in PIPF 004 and PIPF 006 the mortality rate with Esbriet 2403 mg/day group was 7.8% compared with 9.8% with placebo (HR 0.77 [95% CI, 0.47–1.28]).

In study PIPF-016, the decline in percent predicted FVC from baseline at Week 52 of treatment was significantly reduced in patients receiving Esbriet (N = 278) compared with patients receiving placebo (N = 277; p<0.000001, rank ANCOVA). Treatment with Esbriet also significantly reduced the decline in percent predicted FVC from baseline at Weeks 13 (p < 0.000001), 26 (p < 0.000001), and 39 (p = 0.000002). At Week 52, a decline from baseline in percent predicted FVC of ≥10% or death was seen in 17% of patients receiving Esbriet compared to 32% receiving placebo (Table 5).

Table 5: Categorical Assessment of Change from Baseline to Week 52 in Percent Predicted FVC in Study PIPF-016

	Pirfenidone 2403 mg/day (N = 278)	**Placebo (N = 277)**
Decline of ≥10% or death	46 (17%)	88 (32%)
Decline of less than 10%	169 (61%)	162 (58%)
No decline (FVC change >0%)	63 (23%)	27 (10%)

The decline in distance walked during a 6MWT from baseline to Week 52 was significantly reduced in patients receiving Esbriet compared with patients receiving placebo in PIPF-016 (p=0.036, rank ANCOVA); 26% of patients receiving Esbriet showed a decline of ≥50 m in 6MWT distance compared to 36% of patients receiving placebo.

In a pre-specified pooled analysis of studies PIPF-016, PIPF-004, and PIPF-006 at Month 12, all-cause mortality was significantly lower in Esbriet 2403 mg/day group (3.5%, 22 of 623 patients) compared with placebo (6.7%, 42 of 624 patients), resulting in a 48% reduction in the risk of all-cause mortality within the first 12 months (HR 0.52 [95% CI, 0.31–0.87], p = 0.0107, log-rank test).

5.2 Pharmacokinetic properties

Absorption

Administration of Esbriet capsules with food results in a large reduction in Cmax (by 50%) and a smaller effect on AUC, compared to the fasted state. Following oral administration of a single dose of 801 mg to healthy older adult volunteers (50–66 years of age) in the fed state, the rate of pirfenidone absorption slowed. The AUC in the fed state was approximately 80–85% of the AUC observed in the fasted state.

A reduced incidence of adverse events (nausea and dizziness) was observed in fed subjects when compared to the fasted group. Therefore, it is recommended that Esbriet be administered with food to reduce the incidence of nausea and dizziness.

Bioequivalence was demonstrated in the fasted state when comparing the 801 mg tablet to three 267 mg capsules. In the fed state, the 801 mg tablet met bioequivalence criteria based on the AUC measurements compared to the capsules, while the 90% confidence intervals for Cmax (108.26% - 125.60%) slightly exceeded the upper bound of standard bioequivalence limit. The effect of food on pirfenidone exposure was consistent between the tablet and capsule formulations.

The absolute bioavailability of pirfenidone has not been determined in humans.

Distribution

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). Mean apparent oral steady-state volume of distribution is approximately 70 L, indicating that pirfenidone distribution to tissues is modest.

Biotransformation
In vitro metabolism studies with hepatic microsomes indicate that pirfenidone is metabolized primarily via CYP1A2 with lesser contribution from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1. In vitro and in vivo studies to date have not detected any activity of the major metabolite (5-carboxy-pirfenidone), even at concentrations or doses greatly above those associated with activity of pirfenidone itself.

Elimination
The oral clearance of pirfenidone appears modestly saturable. In a multiple dose, dose ranging study in healthy older adults administered doses ranging from 267 mg to 1335 mg three times a day, the mean clearance decreased by approximately 25% above a dose of 801 mg three times a day. Following single dose administration of pirfenidone in healthy older adults, the mean apparent terminal elimination half-life was approximately 2.4 hours. Approximately 80% of an orally administered dose of pirfenidone is cleared in the urine within 24 hours of dosing. The majority of pirfenidone is excreted as the 5-carboxy-pirfenidone metabolite (>95% of that recovered), with less than 1% of pirfenidone excreted unchanged in urine.

Pharmacokinetics in Special Populations

Renal impairment
No clinically relevant differences in the pharmacokinetics of pirfenidone were observed in subjects with mild to severe renal impairment compared with subjects with normal renal function. The parent substance is predominantly metabolised to 5 carboxy-pirfenidone, for which pharmacodynamics and safety margins were not established. The $AUC_{0-\infty}$ of 5-carboxy-pirfenidone was significantly higher in the moderate ($p=0.009$) and severe ($p<0.0001$) renal impairment groups than in the group with normal renal function. The predicted amount of metabolite accumulation at steady state is not pharmacodynamically important because the terminal elimination half-life is only 1–2 hours in these subjects and there is no or minimal pharmacologic activity of the metabolite as measured by TNF inhibitory effects.

Hepatic impairment
The pharmacokinetics of pirfenidone and the 5-carboxy-pirfenidone metabolite were compared in subjects with moderate hepatic impairment (Child Pugh Class B) and in subjects with normal hepatic function. Results showed that there was a mean increase of 60% in pirfenidone exposure after a single dose of 801 mg pirfenidone (3 x 267 mg capsule) in patients with moderate hepatic impairment. Pirfenidone should be used with caution in patients with mild to moderate hepatic impairment and patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see section 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

In repeated dose toxicity studies increases in liver weight were observed in mice, rats and dogs; this was often accompanied by hepatic centrilobular hypertrophy. Reversibility was observed after cessation of treatment. An increased incidence of liver tumours was observed in carcinogenicity studies conducted in rats and mice. These hepatic findings are consistent

with an induction of hepatic microsomal enzymes, an effect which has not been observed in patients receiving Esbriet. These findings are not considered relevant to humans.

A statistically significant increase in uterine tumours was observed in female rats administered 1500 mg/kg/day, 37 times the human dose of 2403 mg/day. The results of mechanistic studies indicate that the occurrence of uterine tumours is probably related to a chronic dopamine-mediated sex hormone imbalance involving a species specific endocrine mechanism in the rat which is not present in humans.

No adverse effects on fertility were observed in preclinical studies. In animals placental transfer of pirfenidone and/or its metabolites occurs with the potential for accumulation of pirfenidone and/or its metabolites in amniotic fluid. At high doses (≥450 mg/kg/day) rats exhibited a prolongation of estrous cycle and a high incidence of irregular cycles. At high doses (≥1000 mg/kg/day) rats exhibited a prolongation of gestation and reduction in foetal viability. Studies in lactating rats indicate that pirfenidone and/or its metabolites are excreted in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk. Reproductive toxicology studies demonstrated no adverse effects on male and female fertility or postnatal development of offspring in rats and there was no evidence of teratogenicity in rats (1000 mg/kg/day) or rabbits (300 mg/kg/day).

Pirfenidone showed no indication of mutagenic or genotoxic activity in a standard battery of tests and when tested under UV exposure was not mutagenic. When tested under UV exposure pirfenidone was positive in a photoclastogenic assay in Chinese hamster lung cells.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Microcyrstalline cellulose
Croscarmellose sodium
Povidone
Magnesium stearate

Capsule shell
Titanium dioxide
Gelatin

Printing Inks
Opacode brown S-1-16530 containing:
Shellac
Iron oxide black)
Iron oxide red
Iron oxide yellow
Propylene glycol
Ammonium hydroxide.

Tablet core
Microcrystalline cellulose
Croscarmellose sodium
Povidone K30

Colloidal anhydrous silica
Magnesium stearate

Film coat
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc

267 mg tablet
Iron oxide yellow (E172)

534 mg tablet
Iron oxide yellow (E172)
Iron oxide red (E172)

801 mg tablet
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Capsules and tablets 267mg and 801mg: 48 months.

Tablet 534mg: 24 months

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

High-Density Polyethylene (HDPE) bottle with a child-resistant and tamper-evident screw cap

Pack sizes

267mg hard capsules
1 bottle containing 270 capsules

267 mg film-coated tablets
1 bottle containing 90 film-coated tablets

534 mg film-coated tablets
1 bottle containing 90 film-coated tablets

801 mg film-coated tablets
1 bottle containing 90 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

9. DATE OF FIRST APPROVAL

Esbriet 267mg capsules - 23 June 2016

Esbriet 267mg, 534mg and 801 mg tablets – 29 March 2018

10. DATE OF REVISION OF THE TEXT

9 August 2022

Summary of Changes Table

Section Changed	Summary of new information
Section 4.8	Minor Editorial Changes to Tables 1 and 2 to align with the latest version of the CDS (version 11.0).