PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Esbriet® 267

Esbriet® 801

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Esbriet contains pirfenidone as the active substance.

Each film-coated tablets contains 267 mg and 801 mg pirfenidone

Sugar free

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Esbriet 267 mg film-coated tablets are yellowish white to pale yellow, oval, biconvex film-coated tablets, debossed with“PFD” on one side.

Esbriet 801 mg film-coated tablets are greyish brown to brownish red, oval, biconvex film-coated tablets, debossed with “PFD” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Esbriet is indicated for the reduction of progression of mild to moderately severe idiopathic pulmonary fibrosis (IPF) in non-smoking and former-smoking adults.

4.2 Posology and method of administration

Posology

Adults

The recommended daily dose of Esbriet for patients with IPF is 801 mg three times a day with food, for a total of 2 403 mg/day.

Upon initiating treatment, the dose should be titrated to the recommended daily dose of 2 403 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 (1 602 mg/day)
- Day 15 onward: a dose 801 mg three times a day (2 403 mg/day)

Doses above 2 403 mg/day are not recommended for any patient.

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

Patients who experience intolerance to therapy due to gastrointestinal side effects should be reminded to take Esbriet with food. If symptoms persist, the dose of Esbriet may be reduced to 267 mg - 534 mg 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 Special warnings and precautions for use*). 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 Special warnings and precautions for use*). Once the rash has resolved, Esbriet may be reintroduced and re-escalated up to the recommended daily dose at the discretion of the doctor.

Hepatic function

If a patient exhibits an aminotransferase elevation > 3 to < 5 x ULN without bilirubin elevation after starting Esbriet therapy, other causes should be excluded, and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered. If clinically appropriate, the dose of Esbriet should be reduced or interrupted.

Once liver function tests are within normal limits Esbriet may be re-escalated to the recommended daily dose if tolerated. If a patient exhibits an aminotransferase elevation >3 to < 5 x ULN accompanied by hyperbilirubinemia or clinical signs or symptoms indicative of liver injury, Esbriet should be discontinued and the patient should not be re-challenged.

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

Special Dosage Instructions

Elderly

No dose adjustment is necessary in patients 65 years and older *(see section 5)*.

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 Esbriet 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 (*see sections 4.5 and 5.2*). Esbriet has not been

studied and is not recommended in patients with severe hepatic impairment or end stage liver disease, (*see sections 4.4 and 5.2*). It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations (*see sections 4.2, 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 (CrCl 30-50 mL/min) to severe (CrCl <30 mL/min) renal impairment. Esbriet has not been studied and is not recommended in patients with end-stage renal disease requiring dialysis (*see sections 4.2 and 5.2*).

Method of Administration

Esbriet is to be swallowed whole with water and taken with food to reduce the possibility of nausea and dizziness.

4.3 Contraindications

- Hypersensitivity to pirfenidone or to any of the excipients of Esbriet.
- Concomitant use of fluvoxamine (*see section 4.5*).
- History of angioedema with Esbriet (*see section 4.4*).
- Concomitant use of strong Cytochrome P450 CYP 1A2 inducers, including cigarette smoking.
- Severe hepatic impairment or end stage liver disease (*see sections 4.2 and 4.4*).
- Severe renal impairment (CrCl <30 mL/min) or end stage renal disease requiring dialysis (*see sections 4.2 and 4.4*).

4.4 Special warnings and precautions for use

General

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. 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 minimised 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 medical practitioner. Dose adjustments or temporary treatment discontinuation may be necessary for photosensitivity reaction or rash (*see section 4.2*). Caution is advised if Esbriet is used concomitantly with medicines that can cause photosensitivity.

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 Esbriet in

the post-marketing setting. Therefore, patients who develop signs and symptoms of angioedema following administration with 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 (*see section 4.3 Contraindications*).

Use in Special Populations

Renal Impairment

See (*sections 4.2 and 5.2*).

Hepatic Impairment

See (*sections 4.2 and 5.2*).

Paediatric use

Safety and effectiveness of Esbriet in paediatric patients has not been established.

4.5 Interaction with other medicines and other forms of interaction

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

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 discontinue use of strong inducers of CYP1A2 and to stop smoking before and during treatment with pirfenidone (*see section 4.3*).

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 Esbriet 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 sections 4.2 and 4.4*).

Co-administration of Esbriet and 750 mg of ciprofloxacin (a moderate and selective inhibitor of CYP1A2) increased the exposure to Esbriet by 81 %. If ciprofloxacin at the dose of 750 mg twice daily cannot be avoided, the dose of Esbriet should be reduced to 1 602 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.

Cigarette Smoking and Inducers of CYP1A2

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(*see section 4.3*). 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 medicines that act as potent inducers of both CYP1A2 and the other CYP isoenzymes involved in the metabolism of Esbriet (e.g., rifampicin) may

result in significant lowering of Esbriet plasma levels. These medicines should be avoided whenever possible.

4.6 Fertility, pregnancy and lactation

Pregnancy

Esbriet should not be taken during pregnancy.

Breastfeeding

Mothers should not breastfeed their infants when taking Esbriet.

4.7 Effects on ability to drive and use machines

Esbriet may cause dizziness and fatigue, which could influence the ability to drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile:

Clinical Trials

The safety of Esbriet has been evaluated in 623 patients from three Phase 3 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).

b. Tabulated list of adverse reactions

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

ADR (MedDRA)	Esbriet (n = 623)	

Study Duration	52-72 weeks	
System Organ Class	All grades (%)	Frequency Category
Metabolism and Nutrition Disorders		
Decreased weight	10,1 %	Very common
Decreased appetite	20,7%	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		
Increased ALT	3,2 %	Common
Increased AST	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		
Fatigue	26,0 %	Very common
Asthenia	6,4 %	Common

Post Marketing

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

System Organ Class	**Adverse Drug Reaction (Only use the 2 columns)**
Blood and Lymphatic System Disorders	Agranulocytosis

Immune System Disorders	Angioedema
Hepatobiliary Disorders	Bilirubin increased in combination with increases of ALT and AST
	Clinically relevant Drug-Induced Liver Injury, including isolated reports with fatal outcome

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 to SAHPRA via the "6.04 Adverse Drug Reaction Report Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, other immunosuppressants, ATC code: L04AX05.

The mechanism of action of pirfenidone has not been 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).

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

5.2 Pharmacokinetic properties

Absorption

Administration of pirfenidone tablets with food results in a large reduction in C_{max} (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, while the AUC in the fed state was approximately 80 - 85 % of the AUC observed in the fasted state. 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. 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 pirfenidone be administered with food to reduce the incidence of nausea and dizziness.
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.

Metabolism

In vitro metabolism studies with hepatic microsomes indicate that pirfenidone is metabolised 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 1 335 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

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 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 concomitantly taking a known CYP1A2 inhibitor (*see sections 4.2 and 4.4*).

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 compound is predominantly metabolised to 5-carboxy-pirfenidone. 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.

Cigarette Smoking

A Phase 1 interaction study evaluated the effect of cigarette smoking (CYP1A2 inducer) on the pharmacokinetics of pirfenidone. 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 pirfenidone. It is essential that patients given this medicine should stop smoking.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

Tablet contents:

croscarmellose sodium

magnesium stearate

microcrystalline cellulose

povidone K30

Silica, colloidal anhydrous (Colloidal silicon dioxide)

Excipients – Film-coating mixture for tablets:

Iron oxide red (E172, C.I. 77491) for the 801 mg tablets

Iron oxide black (E172, C.I. 77499) for the 801 mg tablets

Iron oxide yellow (E172, C.I. 77492) for the 267 mg tablets

Macrogol 3350 (polyethylene glycol 3350)

Polyvinyl alcohol

Titanium dioxide (E171, C.I. 77891)

Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Esbriet tablets: 48 months

6.4 Special precautions for storage

Store at or below 30 °C in the original container until required for use.

Keep well closed. Store out of reach of children.

This medicine should not be used after the expiry date (EXP) shown on the pack.

6.5 Nature and contents of container

Esbriet 267 and Esbriet 801 film-coated tablets: Square, white 200 mL high-density polyethylene (HDPE) bottles containing 90 tablets with white child-resistant and tamper-evident screw caps with polyethylene inner shell/polypropylene outer shell liners.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park

Building E, Vorna Valley, Midrand

Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S):

Esbriet 267: 56/32.16/0186

Esbriet 801: 56/32.16/0187

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 18 July 2023

10. DATE OF REVISION OF THE TEXT

Last revision: 18 July 2023

Approved Manufacturer

Delpharm Milano S.r.l

Via Carnevale, 1

20054 Segrate (MI)

Italy