Part VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Pirfenidone Newbury (Pirfenidone)

This is a summary of the risk management plan (RMP) for Pirfenidone Newbury. The RMP details important risks of Pirfenidone Newbury, how these risks can be minimized, and how more information will be obtained about Pirfenidone Newbury's risks and uncertainties (missing information).

Pirfenidone Newbury's Summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Pirfenidone should be used.

This summary of the RMP for Pirfenidone Newbury should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Pirfenidone Newbury's RMP

I. The medicine and what it is used for

Pirfenidone Newbury is authorized for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF). It contains pirfenidone as the active substance and it is given by oral administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the PIL and SmPC addressed to patients and Healthcare Professionals
- Important advice on the medicine's packaging.
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status - the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Pirfenidone Newbury is not yet available, it is listed under 'missing information' below.
In the case of Pirfenidone Newbury, these measures are supplemented with additional risk minimization measures mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Pirfenidone Newbury are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential.

Identified risks are concerns for which there is sufficient proof of a link with the use of Pirfenidone Newbury. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Photosensitivity reaction and rash • DILI • Gastrointestinal symptoms
Important potential risks	• Severe skin reactions • Risk of medication error in patients transferring between capsules and tablets
Missing information	• QT Prolongation • Underlying specific cardiac events

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product

Important identified risk: Photosensitivity reaction and rash	
Risk minimisation measures	**Routine risk minimization measures**: Covered under the following section of SmPC and PL Routine risk communication: SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Advice to patients provided in PL in section 2. Listed in PL section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Exposure to direct sunlight (including sunlamps) should be avoided or minimised during treatment with Pirfenidone Newbury Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded to use a sunblock daily and to avoid exposure to the sun, to wear clothing that protects against sun exposure, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to report symptoms of photosensitivity reaction or rash to their physician. Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice (see section 4.4). Once the rash has resolved, Pirfenidone Newbury may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Pirfenidone Newbury is a prescription only medicine. **Additional risk minimization measures:** SmPC PIL Safety Checklist: A Safety Checklist about monitoring and management of photosensitivity reaction and rash was made available to be distributed at the time of launch to all local medical staff involved in managing patients with IPF. It requests reporting of all clinically significant ADRs of photosensitivity reaction and rash to the MAH, where an association is

Important identified risk: Photosensitivity reaction and rash	
	suspected. (Refer Annexure 6) **Routine pharmacovigilance activities:** Adverse reactions reporting and signal detection. **Additional pharmacovigilance activities**: None

Important identified risk: DILI	
Risk minimisation measures	**Routine risk minimization measures:** Covered under the following section of SmPC and PIL **Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Advice to patients provided in PL in section 2. Listed in PL section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** <u>Hepatic function</u> Elevated transaminases have been commonly reported in patients treated with Pirfenidone Newbury. Liver function tests (ALT, AST and bilirubin) should be performed prior to the initiation of treatment with Pirfenidone Newbury, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter (see section 4.8 of the Pirfenidone Newbury SmPC). If a patient exhibits an aminotransferase elevation >3 to <5 ´ ULN without bilirubin elevation and without symptoms or signs of drug induced liver injury after starting Pirfenidone Newbury therapy, other causes should be excluded, and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered. If clinically appropriate, the dose of Pirfenidone Newbury should be reduced or interrupted. Once liver function tests are within normal limits Pirfenidone Newbury may be re-escalated to the recommended daily dose if tolerated.

Important identified risk: DILI	
	Drug-induced liver injury Uncommonly, elevations in AST and ALT were associated with concomitant bilirubin increases. Cases of severe drug-induced liver injury, including isolated cases with fatal outcome, have been reported post-marketing (see section 4.8 of the Pirfenidone Newbury SmPC). In addition to the recommended regular monitoring of liver function tests, prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. If a patient exhibits an aminotransferase elevation >3 to <5 ´ ULN accompanied by hyperbilirubinemia or clinical signs or symptoms indicative of liver injury, Pirfenidone Newbury should be permanently discontinued, and the patient should not be rechallenged If a patient exhibits an aminotransferase elevation to ³5 ´ ULN, Pirfenidone Newbury should be permanently discontinued, and the patient should not be rechallenged. Hepatic impairment In subjects with moderate hepatic impairment (i.e., Child-Pugh Class B), pirfenidone exposure was increased by 60%. Pirfenidone Newbury should be used with caution in patients with pre-existing mild to moderate hepatic impairment (i.e., Child-Pugh Class A and B) given the potential for increased pirfenidone exposure. Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see sections 4.5 and 5.2 of the Pirfenidone Newbury SmPC). Pirfenidone Newbury has not been studied in individuals with severe hepatic impairment and Pirfenidone Newbury must not be used in patients with severe hepatic impairment (see section 4.3 of the Pirfenidone Newbury SmPC) **Other risk minimization measures beyond the Product Information** Medicine's legal status: Pirfenidone Newbury is a prescription only medicine. **Additional risk minimisation measures:** SmPC PIL Safety Checklist A Safety Checklist about monitoring and management of DILI is to be distributed to all local medical staff involved in managing patients with IPF and may be redistributed in case of further updates or launch of new

Important identified risk: DILI	
	formulations. It requests HCPs to report all clinically significant ADRs of liver-related abnormalities to the MAH. (Refer Annexure 6) **Routine pharmacovigilance activities:** Adverse reactions reporting and signal detection. AE follow-up form for DILI adverse reaction **Additional pharmacovigilance activities:** None.

Important identified risk: Gastrointestinal symptoms	
Risk minimisation measures	**Routine risk minimization measures**: **Covered under the following section of SmPC and PIL** **Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.8 (Undesirable effects) Advice to patients provided in PL in section 2. Listed in PL section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** In patients who experience intolerance to therapy due to gastrointestinal undesirable effects, patients should be reminded to take the medicinal product with food. If symptoms persist, the dose of pirfenidone may be reduced to (267 mg two to three times/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. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Pirfenidone Newbury is a prescription only medicine. **Additional risk minimization measures:** None. **Additional pharmacovigilance activities:** None.

Important potential risk: Severe Skin Reactions	
Risk minimisation measures	**Routine risk minimisation measures:** Covered under the following section of SmPC and PIL **Routine risk communication**:

	SmPC: Section 4.8 (Undesirable effects) Advice to patients provided in PL in section 2. Listed in PL section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Treatment initiated and supervised by specialist physicians experienced in the diagnosis and treatment of IPF **Other risk minimization measures beyond the Product Information**: **Pack size**: None **Medicine's legal status**: Pirfenidone Newbury is a prescription only medicine. **Additional risk minimisation measures**: None
Important Potential Risk: Risk of medication error in patients transferring between capsules and tablets	
Risk minimisation measures	**Routine risk minimisation measures** Covered under the following section of SmPC and PIL **Routine risk communication** SmPC: Section 3 (Pharmaceutical Form) Listed in PL section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** The treatment initiated and supervised by specialist physicians experienced in the diagnosis and treatment of IPF. Drug made available through specialty pharmacies The differentiation between dosage forms (capsule vs. tablet) and dosage strengths is aided by the printed component text copy and colour associated with each dosage/strength combination. The capsules and tablets' physical appearance of size, shape, and colour also serves as differentiating characteristic. The capsules and tablets (801 mg) are provided in calendar packs. Other risk minimization measures beyond the Product Information: Pack size: None Medicine's legal status: Pirfenidone Newbury is a prescription only medicine. **Additional risk-minimization measures:** None

	Additional pharmacovigilance activities: None

Missing Information: QT Prolongation	
Risk minimisation measures	**No additional risk minimization measures:** None **Additional pharmacovigilance activities**: None

Missing Information: Underlying Specific Cardiac Events	
Risk minimisation measures	**No additional risk minimization measures:** None **Additional pharmacovigilance activities**: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation.

There are no studies which are conditions of the marketing authorisation or specific obligation of Pirfenidone Newbury.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Pirfenidone Newbury.