Dear Doctor,

Your patient has been prescribed pirfenidone (Esbriet®) tablets (variable dosing) for idiopathic pulmonary fibrosis.

It is not currently clear as to how pirfenidone acts but it is believed to have both anti-fibrotic and anti-inflammatory properties. Pirfenidone is recommended by NICE (Technology Appraisal 282) as an option for the treatment of mild/moderate idiopathic pulmonary fibrosis in adults who have a forced vital capacity of between 50 and 80% predicted.

A brief glance summary of the significant clinical and monitoring issues associated with this drug is enclosed overleaf. The summary of product characteristics and/or BNF should be consulted for further information. Specialist advice regarding drug interactions can be provided by the respiratory specialist pharmacist (0114 2715359 – phone not continually manned) or our medicines information service (0114 2714371). GPs are encouraged to add this as a hospital issued drug in order to pick up potential interactions. There is a useful reminder on how to do this for GP practices on the intranet.

Written information on how to take the tablets has been provided and counselling given at the hospital. The medication is provided and monitored through an initiation and subsequently maintenance phase to reduce side effects of rash, nausea, vomiting, diarrhoea, skin sensitisation to sunlight and liver function derangement. Sheffield Teaching Hospitals (STH) Interstitial Lung Disease (ILD) specialist nurse coordinates drug initiation, maintenance therapy and blood monitoring. Patients are provided with contact details (Phone No 01142269758). We would be grateful if you could add Factor 50 sunblock to your patient's repeat prescription.

Pirfenidone is funded by NHS England through a specialised service/drug arrangement and is prescribed by the STH ILD service within the department of respiratory medicine at the Northern General Hospital. The medication is delivered to the patient via a homecare delivery company. Hence you will not be asked to issue prescriptions for this medicine. Their usual repeat medicines should continue as usual. We will write to you again if treatment with pirfenidone is stopped so that this can be removed from the patient's record and we will also inform you of any other medication changes by letter.

If you have any queries regarding this or any aspect of their treatment, please do not hesitate to contact Dr Stephen Bianchi, Consultant Respiratory Physician, Northern General Hospital, STH on 01142714279.

Yours faithfully

Brief glance summary of prescribing and monitoring issues for Pirfenidone (Esbriet®)

Please refer to the BNF and summary of product characteristics for full details

Issue	Notes and monitoring	Monitoring responsibility
Hepatic function	Elevations in ALT and AST >3 × upper limit of normal (ULN) have been reported. Rarely these have been associated with concomitant elevations in total serum bilirubin. Liver function tests (ALT, AST and bilirubin) should be conducted prior to the initiation of treatment with Esbriet, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter. *Recommendations in case of ALT/AST elevations* If a patient exhibits an aminotransferase elevation to >3 to ≤5 x ULN after starting Esbriet therapy, confounding medicinal products should be discontinued, other causes excluded, and the patient monitored closely. If clinically appropriate the dose 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 ≤5 x ULN accompanied by symptoms or hyperbilirubinaemia, Esbriet should be discontinued and the patient should not be rechallenged. If a patient exhibits an aminotransferase elevation to >5 x ULN, Esbriet should be discontinued and the patient should not be rechallenged. *Hepatic impairment* Esbriet should be used with caution in patients with pre-existing mild to moderate hepatic impairment (i.e. Child-Pugh Class A and B). Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor. Esbriet has not been studied in individuals with severe hepatic impairment and should not be used in patients with severe hepatic impairment.	ILD team (STH) Primary care to be aware and liaise with STH if necessary
Photosensitivity reaction and rash	Exposure to direct sunlight (including sunlamps) should be avoided or minimised during treatment. Patients should be instructed to use a sunblock daily, to wear clothing that protects against sun exposure, and to avoid	ILD team (STH) and primary care

	other medicinal products known to cause photosensitivity. Patients should be instructed to report symptoms of photosensitivity reaction or rash to their doctor. Severe photosensitivity reactions are uncommon. Dose adjustments or temporary treatment discontinuation may be necessary in mild to severe cases of photosensitivity reaction or rash.	
Dizziness	Dizziness has been reported in patients taking Esbriet. Therefore, patients should know how they react to this medicinal product before they engage in activities requiring mental alertness or coordination. In clinical studies, most patients who experienced dizziness had a single event, and most events resolved, with a median duration of 22 days. If dizziness does not improve or if it worsens in severity, dose adjustment or even discontinuation may be warranted.	ILD team (STH) and primary care
Fatigue	Fatigue has been reported in patients taking Esbriet. Therefore, patients should know how they react to this medicinal product before they engage in activities requiring mental alertness or coordination.	ILD team and primary care
Weight loss	Weight loss has been reported in patients treated with Esbriet. Physicians should monitor patients' weight, and when appropriate encourage increased caloric intake if weight loss is considered to be of clinical significance.	ILD team and primary care
Pharmacokinetic drug interactions	Approximately 70–80% of pirfenidone is metabolised via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1. Consumption of grapefruit juice is associated with inhibition of CYP1A2 and should be avoided during treatment with pirfenidone. Esbriet is contraindicated in patients with concomitant use of fluvoxamine which should be discontinued prior to the initiation of, and avoided during treatment.. Other therapies that are inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone (e.g. CYP2C9, 2C19, and 2D6) should be avoided during pirfenidone treatment. *In vitro in vivo* extrapolations indicate that strong and selective inhibitors of CYP1A2 (e.g. enoxacin) 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 (one capsule, three times a day). Patients should be closely monitored for emergence of adverse reactions associated with Esbriet therapy. Discontinue Esbriet if necessary.	ILD team (STH) Primary care to be aware and liaise with STH if necessary

	Co-administration of Esbriet and 750 mg of ciprofloxacin (a moderate 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 (two capsules, 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 (e.g. amiodarone, propafenone). Special care should also be exercised if CYP1A2 inhibitors are being used concomitantly with potent inhibitors of one or more other CYP isoenzymes involved in the metabolism of pirfenidone such as CYP2C9 (e.g. amiodarone, fluconazole), 2C19 (e.g. chloramphenicol) and 2D6 (e.g. fluoxetine, paroxetine). <u>Cigarette smoking and inducers of CYP1A2</u> The exposure to pirfenidone in smokers was 50% of that observed in non-smokers. 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. 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.	