Information Guideline for Local Hospitals and GPs. Pirfenidone for idiopathic pulmonary fibrosis

1. Introduction

Pirfenidone is an anti-fibrotic used for the treatment of Idiopathic Pulmonary Fibrosis

All patients who are to be considered for pirfenidone must be discussed at the Hull ILD MDT. It can then recommend as an option for treating idiopathic pulmonary fibrosis in line with the criteria as set out in NICE Technology Appraisal 282 and NICE Clinical Guideline 163, e.g. if:

- The patient has a forced vital capacity (FVC) between 50% and 80% predicted and
- The manufacturer provides pirfenidone with the discount agreed in the patient access scheme.

Treatment should be discontinued if there is evidence of disease progression, defined as a decline in predicted FVC of 10% or more within any 12 month period or if the patient is unable to tolerate Pirfenidone due to side effects.

Pirfenidone is a Red drug and will be prescribed and supplied by the specialist team.

2. Abbreviations

ILD – Interstitial Lung Disease
FVC – forced vital capacity
FEV1 – forced expiratory volume in 1 second
UIP – Usual Interstitial Pneumonia
IPF – Idiopathic Pulmonary Fibrosis
MDT – Multi-Disciplinary Team
GP – General Practitioner
6MWT – six minute walk test

3. Dose and Administration

Upon initiating treatment, the dose should be titrated to the recommended daily dose of nine capsules per day over a 28-day period as follows:

- Days 1 to 14: one capsule (267 mg) three times a day (801 mg/day)
- Days 15 to 28: two capsules (534 mg) three times a day (1602 mg/day)
- Day 29 onward: three capsules (801 mg) three times a day (2403 mg/day)

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

Doses above 2403 mg/day are not recommended for any patient.

Patients who miss 14 consecutive days or more of treatment should re-initiate therapy by undergoing the initial 4-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.

A dose reduction of pirfenidone to 2 capsules (534 mg) three times daily is required with concomitant use of high dose ciprofloxacin (750mg twice daily). For this reason concomitant use of ciprofloxacin should be avoided & a discussion with the specialist hospital should be had if no alternative exists.

Further information can be found in the Summary of Product Characteristics - Pirfenidone & Policy "Pirfenidone – Treatment of Idiopathic Pulmonary Fibrosis"

4. Adverse Effects

The summary of product characteristics lists the following adverse reactions for pirfenidone as the most commonly reported (10% or higher): nausea, rash, fatigue, diarrhoea, dyspepsia and photosensitivity reaction.

Very common side effects (may affect more than 1 in 10 people)

Side Effect	Action	
	By local hospital / GP	By specialist hospital
Gastro-intestinal disturbances- nausea, diarrhoea, indigestion.	• Advise to take with food. Prescribe anti – reflux therapy. If symptoms persist discuss with specialist hospital	• Reduce dose to 1 or 2 capsules 3 times a day with food; re-escalate as tolerated. • If symptoms persist interrupt treatment for 7 days and restart.
Photosensitivity reaction / skin rash	• Discuss with the specialist hospital. • Advise to use factor 50 sun block • Advise to avoid sun exposure. • Avoid use of drugs that may cause photosensitive skin rash eg Doxycycline	• Reduce dose to 1 capsule TDS • If rash persists after 7 days stop taking drug for 15 days and then re-escalate as per initial titration scheme. • If reaction is severe, stop Pirfenidone and consider treatment for rash
Hepatic impairment – bruising, itchy skin, loss of appetite, dark urine.	• Discuss with specialist hospital. • Monitor liver function as per SCG (section 10)	• Review as appropriate undertaking dose adjustment/discontinuation in accordance with policy
Weight loss	• Monitor – encourage increase in calories • Report sudden weight loss to specialist hospital	• Review as appropriate
Tiredness	• Encourage rest • Contact specialist hospital if overwhelming tiredness occurs	• Review as appropriate • Consider dose reduction
Headache	• Manage with occasional simple analgesia • Contact specialist hospital if severe / frequent	• Review as appropriate
In case of any severe or life threatening side effect	• Immediately stop Pirfenidone and contact specialist hospital	• Review as appropriate

Common side effects (may affect up to 1 in 10 people)

- Infections of the throat or airways going into the lungs and / or sinusitis
- Bladder infections
- Weight loss
- Difficulty sleeping
- Dizziness
- Feeling sleepy
- Changes in taste
- Hot flushes
- Shortness of breath
- Cough
- Stomach problems such as acid reflux, vomiting, feeling bloated, abdominal pain and discomfort, heart burn, feeling constipated and passing wind
- Blood tests may show increased levels of enzymes
- Skin problems such as itchy skin, skin redness or red skin, dry skin, skin rash

- Muscle pain, aching joints /joint pains
- Feeling weak or feeling low in energy
- Chest pain
- Sunburn

Uncommon side effects (may affect up to 1 in 100 people)
- Swelling of the face, lips and/ or tongue
- Difficulty breathing or wheezing

Rare side effects (may affect up to 1 in 100 people)
- Blood tests may show decrease in white blood cells

Further information can be found in the Summary of Product Characteristics.

5. Cautions
- Concomitant use with Ciprofloxacin – reduce dose of pirfenidone to 2 capsules (534 mg) 3 times a day with high dose ciprofloxacin (750mg twice daily). Discuss with the specialist Hospital if no alternative to ciprofloxacin exists.
- Omeprazole and rifampicin may reduce the efficacy of pirfenidone
- Avoid exposure to direct sunlight
- Avoid consumption of grapefruit juice

6. Contraindications
- Hypersensitivity to the active substance within the drug or its excipients
- History of angioedema with pirfenidone
- Concomitant use of fluvoxamine
- Severe hepatic impairment or end stage liver disease
- Severe renal impairment (CrCl <30 ml/min) or end stage renal disease requiring dialysis
- Smoking

Further information can be found in the Summary of Product Characteristics

7. Interactions
- Avoid exposure to direct sunlight
- Several CYP enzymes are involved in the metabolism of pirfenidone, CYP1A2 being the most prominent CYP enzyme involved. Strong inducers and inhibitors of these enzymes may result in a reduced or increased exposure to pirfenidone, examples include ciprofloxacin (dose of pirfenidone to be reduced) and fluvoxamine (should be avoided), and smoking.
- Not all interactions noted in the SPC are likely to be clinically significant and not all inducers and inhibitors are mentioned by name. Advice from the specialist hospital is therefore required.
- When in doubt, GPs and local hospitals are advised to seek the advice of the specialist hospital.

Contraindicated – fluvoxamine

- **Avoid concomitant use with:**

Carbamazepine	Isoniazid	Phenytoin
Cimetidine	Nalidixic-acid	Primidone
Ciprofloxacin – see section 3. Dosing	Norfloxacin	Rifampicin
Clarithromycin	Oral-contraceptives	Ritonavir
Enoxacin	Phenobarbital	St Johns Wort
Erythromycin		

- **Use with caution:**

Amiodarone	Diltiazem	Insulin	Nicotine	Sertraline
Amitriptyline	Disulfiram	Lansoprazole	Omeprazole	Zafirlukast
Aprepitant	Duloxetine	Levofloxacin	Paroxetine	Topiramate
Bupropion	Entacapone	Ketoconazole	Probencid	Moxifloxacin
Chloramphenicol	Ethylestradiol	Methoxsalen	Propafenone	Fluvastatin
Cinacalcet	Fenofibrate	Metronidazole	Quinidine	Diclofenac
Citalopram	Fluconazole	Mexiletine	Sildenafil	
Clozapine	Fluoxetine	Modafinil	Terbinafine	

Further information can be found in the Summary of Product Characteristics.

8. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

- Monitor for side effects as described in section 4 and treat / advise as appropriate.
- GPs and local hospitals to inform specialist hospital as per contacts below if patient is suffering from any side effects.

Local hospitals (NLAG/York) to monitor Hepatic Function (ALT/ AST/Alk Phos / Bilirubin): every 3 months and relay results back to Hull. There is no responsibility for GPs to perform phlebotomy or monitor blood results).

- If the **AST is more than 3 times upper limit (and less than 5 times upper limit)** after starting pirfenidone then:
    - Contact the ILD Team in the specialist hospital for advice who will manage as per policy

- If the **AST is less than or equal to 5 times upper limit** after starting pirfenidone **together with hyperbilirubinaemia and symptoms** then:
    - Discontinue treatment and contact the ILD team in the specialist hospital who will manage as per policy

- If the **AST is more than 5 times** then:
    - Discontinue treatment and contact the ILD team in the specialist hospital who will manage as per policy

9. Responsibilities

a. Specialist Hospital:

- Prescribe medication and arrange supplies
- Diagnosis of ILD in line NICE TAG282, Clinical Guideline 163 and Specialist Service Specifications
- Send a letter to the local hospital (NLAG/York) and GP to communicate diagnosis and treatment.
- Educate the patient on how to take the medicine and what to do if they feel unwell.
- Prescribe Pirfenidone
- Take blood to monitor liver function at monthly intervals for 6 months and if stable every 3 months thereafter as per Section 8.
- Provide the patient with a blood monitoring booklet for recording results of liver function blood tests
- Arrange for delivery of the medicine
- Review the patient in clinic and via telephone calls
- Provide the patient with contact information should they require.

- Inform the GP and local hospital after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP and local hospital of patients who do not attend clinic appointments.
- To provide any advice to the patient/carer/GP/local hospital when requested.
- Report adverse effects to the Yellow Card Scheme
- To continue blood monitoring if local hospital/GP can't provide monitoring (not signed up to enhanced contract).

b. Local Hospital and GPs <u>(if signed up to enhanced contract):</u>

- Ensure Pirfenidone is added to the patient's SCR in the hospital only/3rd party prescriber section (CCG medicines management team can provide details of how to do this for both SystemOne & EMIS web- if this process is unfamiliar).
- Local Hospital (NLAG/York) to review patient and take blood to monitor liver function at 3 monthly intervals as per Section 8 and relay results back to Hull. No blood monitoring or phlebotomy required from the GP.
- Inform the specialist hospital in writing if unable to comply with monitoring requirements
- Communicate results to the patients, results to be recorded in the 'Blood Monitoring Booklet'
- Ensure no interacting medication is prescribed without liaising with the specialist team first.
- Report any adverse events to the specialist hospital as outlined in sections 4 & 8, where appropriate
- Request advice from the specialist hospital when necessary.
- To ensure drug interactions & potential adverse effects of Pirfenidone are considered during consultations

c. Patient or parent/carer:

- Hold responsibility for their 'Blood monitoring Booklet' – to record their blood test results and bring to each clinic appointment.
- Attend appointments for the scheduled blood tests to be taken.
- Report to the specialist hospital, GP or local hospital if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant).
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist, shared care/spoke hospital or GP.

10. Contact numbers for advice and support

Dr Simon Hart Secretary 01482 624067
Specialist Nurses Mark Major and Amanda Bell 01482 622409

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