RED GUIDANCE FOR PIRFENIDONE FOR PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS.

1. Background

Pirfenidone is an anti-fibrotic used for the treatment of Idiopathic Pulmonary Fibrosis. Pirfenidone has been shown to slow the rate of progression in IPF.

It is recommended to add pirfenidone to patients' records as a red drug as per local SOPs; to aid with drug-drug interaction checking.

2. Indication

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 504, 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

3. Dose/Duration

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. 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

5. 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.

Adverse effects	Action for GP
Gastro-intestinal disturbancesnausea, diarrhoea, indigestion.	Advise to take with food. Prescribe anti – reflux therapy. Anti diarrhoeal medication i.e. Loperamide. If symptoms persist discuss with specialist hospital
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 e.g. Doxycycline
Hepatic impairment – bruising, itchy skin, loss of appetite, dark urine.	Discuss with specialist hospital. Monitor liver function as per SCG (section 10)
Weight loss	Monitor – encourage increase in calories. Report sudden weight loss to specialist hospital
Tiredness	Encourage rest Contact specialist hospital if overwhelming tiredness occurs
Headache	Manage with occasional simple analgesia Contact specialist hospital if severe / frequent
In case of any severe or life threatening side effect	Immediately stop Pirfenidone and contact specialist hospital

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.

6. Drug interactions

- 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.
- Avoid exposure to direct sunlight

Contraindicated – fluvoxamine

The following drugs are known or suspected interactions:	
Interacting Drug	Advice
Carbamazepine	Avoid
Cimetidine	Avoid
Cimetidine	Avoid
Clarithromycin	Avoid
Enoxacin	Avoid
Erythromycin	Avoid
Isoniazid	Avoid
Nalidixic-acid	Avoid
Norfloxacin	Avoid
Oral-contraceptives	Avoid
Phenobarbital	Avoid
Phenytoin	Avoid
Primidone	Avoid
Rifampicin	Avoid
Ritonavir	Avoid
St Johns Wort	Avoid

- **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.

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

- Monitor for side effects as described in section 4 and treat /advice 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

7. Pregnancy and Lactation

Data on use in pregnant patients is insufficient to inform on drug associated risks for major birth defects and miscarriage.

A decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

Excreted into human milk: Unknown
Excreted into animal milk: Yes

8. Information for patient

Patient or parent/carer:

- 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.

https://www.medicines.org.uk/emc/product/3705/pil#gref

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