22 May 2014
EMA/CHMP/127991/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Esbriet

International non-proprietary name: pirfenidone

Procedure No. EMEA/H/C/002154/II/0016

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, InterMune UK Ltd. submitted to the European Medicines Agency on 1 October 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Esbriet	pirfenidone	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The MAH proposed the update of section 4.8 of the SmPC to include agranulocytosis as a rare event as a result of post marketing surveillance. The Package Leaflet was proposed to be updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Greg Markey

1.2. Steps taken for the assessment

Submission date:	1 October 2013
Start of procedure:	20 October 2013
Rapporteur's preliminary assessment report circulated on:	22 November 2013
Rapporteur's updated assessment report circulated on:	12 December 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 December 2013
MAH's responses submitted to the CHMP on:	16 January 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 February 2014
Second request for supplementary information and extension of timetable adopted by the CHMP on:	20 March 2014
PRAC Rapporteur's assessment report regarding PSUR 5 (PSU 007) as endorsed by the PRAC on:	10 April 2014
MAH's responses submitted to the CHMP on:	14 April 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	2 May 2014
Rapporteur's updated assessment report on the MAH's responses circulated on:	21 May 2014
CHMP opinion:	22 May 2014

2. Scientific discussion

2.1. Introduction

Esbriet (pirfenidone) an immunosuppressant, is indicated in adults for the treatment of mild to moderate idiopathic Pulmonary Fibrosis (IPF). The mechanism of action of pirfenidone has not been fully established. However, existing data suggest that pirfenidone exerts both antifibrotic and anti-inflammatory properties.

Esbriet is an Orphan product which was granted a marketing authorization in the EU through the Centralised procedure on 28 February 2011. As of 27 February 2013, Esbriet is commercially available in Austria, Belgium, Canada, Denmark, Finland, France, Germany, Luxembourg, Norway, and Sweden. Esbriet is available through special sales in Spain.

The recommended dose of Esbriet is one 267-mg capsule taken orally with food, three times per day (801 mg) (TID). The dose is gradually increased to three capsules three times per day over the first 14 days of treatment to the recommended maintenance dose of 2403 mg/day.

In April 2012, in response to Esbriet PSUR 1, the European Medicines Agency (EMA) requested that blood dyscrasias be included in the Risk Management Plan (RMP) as an important potential risk and this is being monitored by the Marketing Authorisation Holder (MAH). The fourth Esbriet Periodic Safety Update report (PSUR) was submitted to the EMA on 27 April 2013. That included all suspected Adverse Drug Reactions (ADR) reports received by the Drug Safety Risk Management (DSRM) department at the MAH from 01 September 2012 through 27 February 2013.

The initial scope of the type II variation is to update Section 4.8 of the Summary of Product Characteristics (SmPC) to add “agranulocytosis” following a spontaneous case report (MCN 201306IM003639) received by the MAH from Canada in June 2013 following post-marketing data.

In clinical trials and post-market surveillance, patients treated with pirfenidone have not demonstrated any significant evidence of neutropenia. Chemotoxic agents associated with neutropenia such as antineoplastic drugs, typically show frequency and intensity of neutropenia increasing with length of exposure to the drug. Pirfenidone does not exhibit this pattern as will be described in greater detail below.

The updated SmPC and PL submitted with this variation includes the proposed updated information for which were assessed in parallel in the responses submission for PSUR 5. In the PSUR 5 the MAH provided a review of angioedema/anaphylaxis which described 14 cases of angioedema (two initially reported as anaphylaxis and 1 initially reported as Stevens-Johnson Syndrome, with all 3 considered more likely to be cases of angioedema). All but one of these 14 cases was considered serious, 7 cases involved positive dechallenge and 2 cases involved positive rechallenge. On the basis of this review the MAH proposes to update product information to include ‘angioedema’ as an uncommonly reported ADR (with consequential changes to the Patient Leaflet). In view of the potentially life-threatening nature of these events and the available data regarding reports of angioedema associated with use of pirfenidone, the PRAC agreed that changes to the product information were warranted.

A revised RMP incorporating the changes requested by following PSUR 5 assessment was submitted in May 2014 with the PSUR 6.

2.2. Clinical Safety aspects

2.2.1. Methods – analysis of data submitted

The MAH's clinical development programme for pirfenidone in IPF comprises 13 clinical studies sponsored by the MAH. Across studies included as part of the pirfenidone clinical development programme, 1885 patients or subjects have received study drug, of whom 1175 have received pirfenidone. Overall 334 healthy volunteers and 1551 patients have participated in the MAH's pirfenidone clinical programme.

The MAH presented clinical trial data from the two placebo controlled trials PIPF-004 and PIPF-006 (referred to as the CAPACITY Studies) conducted for a minimum of 72 weeks that treated a total of 779 patients comparing placebo (347 patients) to either a low dose of pirfenidone (1197 mg/d; 87 patients) or the approved dose of pirfenidone (2403 mg/d; 345 patients).

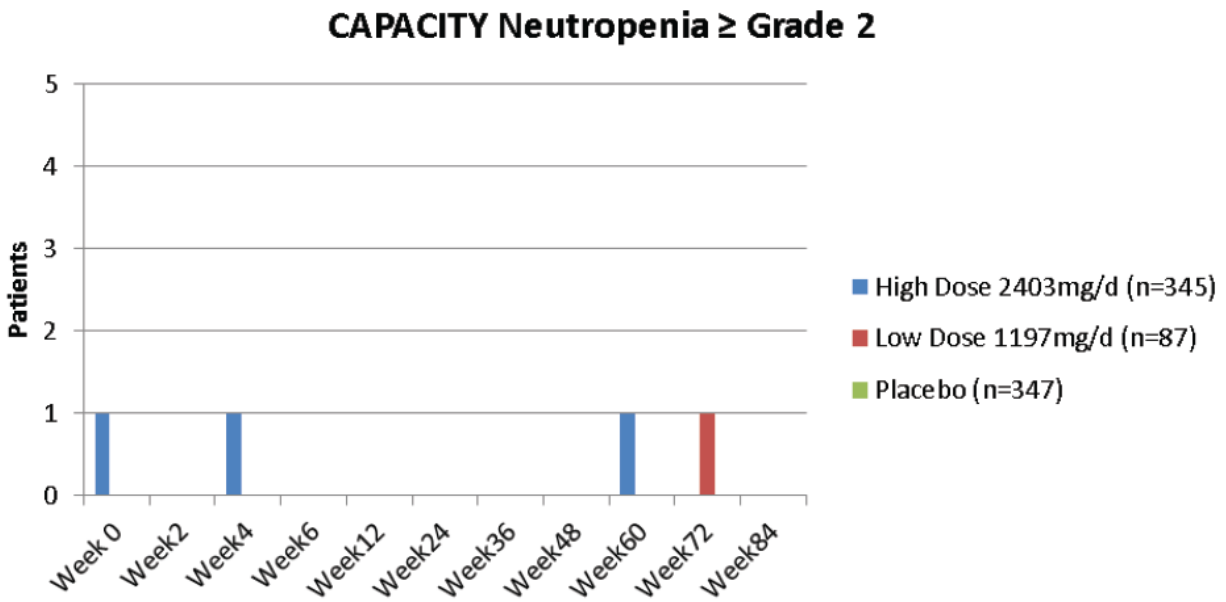
In the most recent PSUR reporting period (31 August 2012 to 27 February 2013), the greatest percentage of ADR reports are being identified from solicited reporting from the post-authorisation safety study (PASSPORT) (31.7% - 195/615) and the Named Patient Programme (NPP) in Europe (32.4% - 199/615) followed by spontaneous reports from Europe and Canada (18.4% - 113/615). This represents a shift from the previous PSUR periods where a majority of the ADR reports originated in Japan.

A post-authorisation safety study involving patients who receive commercial Esbriet, PASSPORT (PIPF-025), enrolled its first patient on 16 February 2012 and has an enrolment of 413 patients as of 13 August 2013.

2.2.2. Results

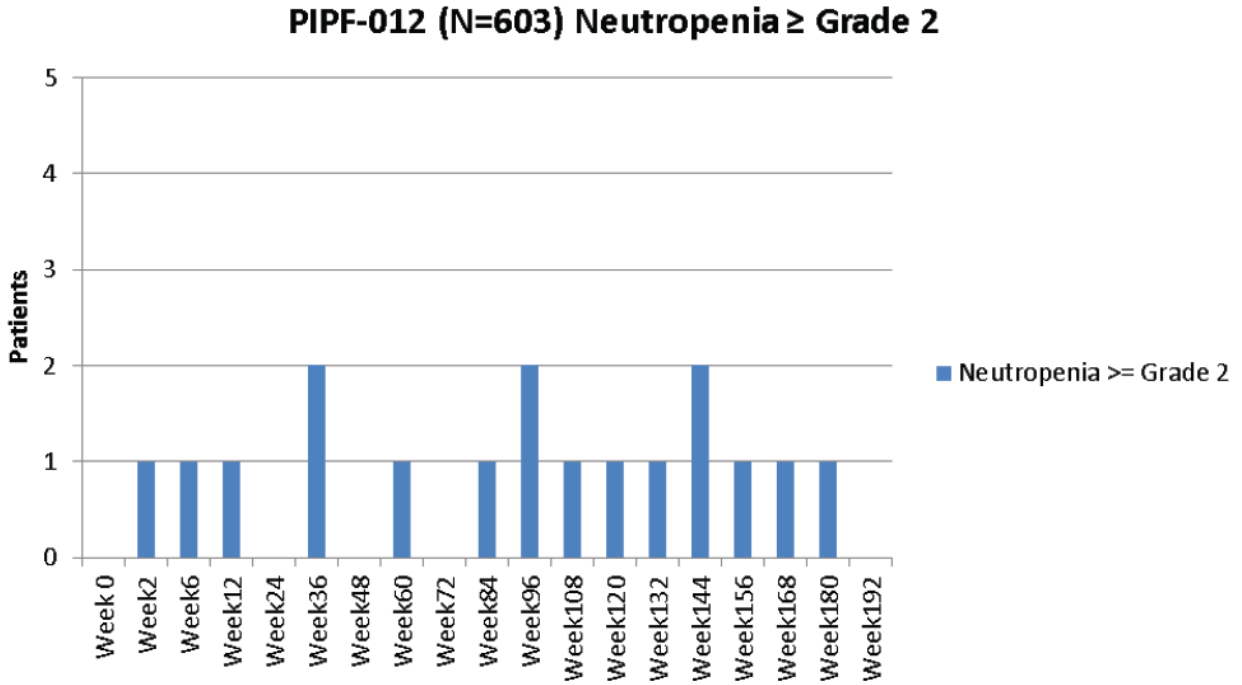
Clinical Trial Data

The MAH presented clinical trial data from the two placebo controlled trials PIPF-004 and PIPF-006 (referred to as the CAPACITY Studies) and stated there were a few instances of neutropenia in the pirfenidone treated patients (Figure 1), one patient at 72 weeks in the 1197 mg/d dose group and one patient at 60 weeks in the 2403 mg/d dose group with Grade 2 neutropenia, in addition to 1 patient with Grade 3 at week 4 in the 2403 mg/d dose group. The fourth patient was neutropenic prior to receiving study drug. These laboratory abnormalities did not result in reported AEs at any single time point.**Figure 1: CAPACITY Patients with Neutropenia ≥ Grade 2 (0-84 weeks)**



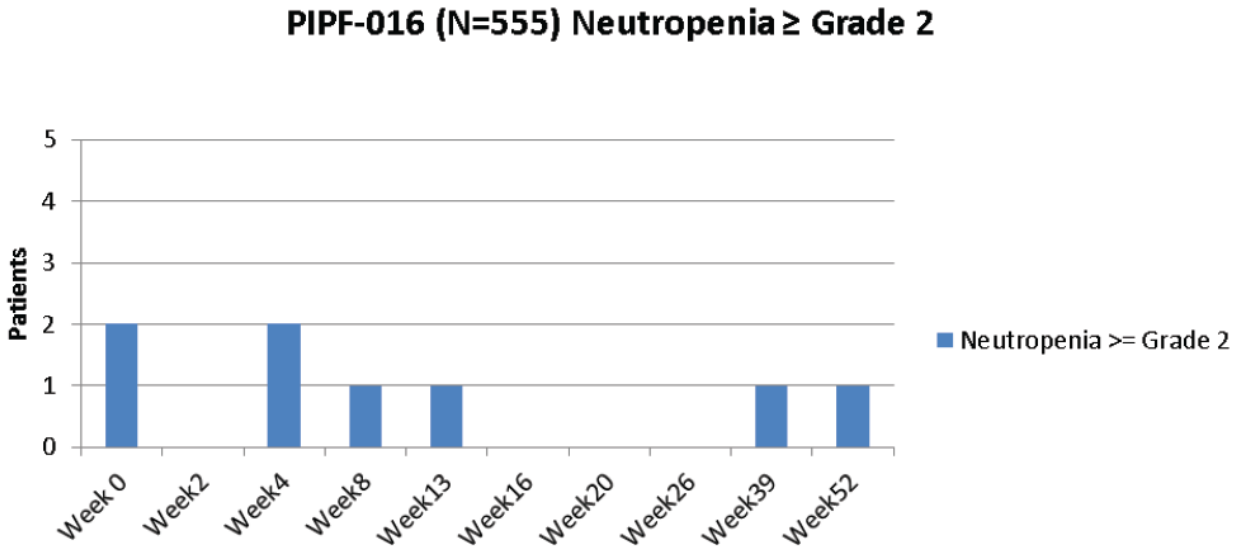
In the ongoing study PIPF-012, the long term open label follow up study that enrolled a total of 603 patients all of whom received the currently approved dose of pirfenidone (2403 mg/d), the frequencies of patients with either Grade 2 or 3 neutropenia was less than 1% out to 180 weeks (Figure 2). There were no events of Grade 4 neutropenia. The patients with Grade 3 neutropenia beyond 108 weeks were individual cases with no evidence to support a causal association. There was one report of pancytopenia with mildly low platelets, anaemia, and leucopenia (MCN201203IM002441) in PIPF-012; however, this patient had been on pirfenidone for more than 3 years before the hematologic abnormalities occurred. A bone marrow biopsy did not reveal any lymphoproliferative disorder and was negative for high grade myelodysplastic syndrome (MDS), although, low grade MDS could not be ruled out. After pirfenidone discontinuation, the patient was diagnosed with iron deficiency anaemia, the platelet count remained in the low normal range, and leucopenia continued. Furthermore, to date there were no SAE reports of neutropenia in PIPF-012.

Figure 2: PIPF 012 Neutropenia ≥ Grade 2 (0 to 180 weeks on PIPF-012)



The MAH stated that a similar pattern is seen in treated patients in another Company sponsored placebo controlled clinical study (designated as ASCEND or PIPF-016) conducted to support the registration in the United States. In this study, a total of 555 patients were randomized 1:1 to either placebo or 2403 mg/d pirfenidone (Figure 3). Since this blinded trial is ongoing, the available safety data combine placebo and pirfenidone treated patients. However, the overall implication is similar to PIPF-12 in that no duration associated neutropenia is occurring in this blinded patient population.

Figure 3: PIPF-016 Neutropenia ≥ Grade 2 (0-52 weeks)



Of the 8 cases of neutropenia (5/848 patients in clinical studies and 3 cases reported spontaneously or from solicited reporting sources; 3700 exposed patients minimum) at least 4 had significant confounding factors to account for this observation; including chemotherapy for malignancy (2 cases) or /myeloproliferative disease (1 case) and Crohn's disease (1 case). A fifth patient without any obvious confounding factors had a single episode of neutropenia reported at Week 4 but continued on pirfenidone for another ~ 1.75 years without further neutropenia reported.

In addition and discounting the obvious confounding factors such as malignancy/chemotherapy, the overall frequency of neutropenia of approximately 0.2% (8/4548; rare) of patients exposed to pirfenidone is similar to the overall background rate of neutropenia in the elderly population. The trigger event for the discussion of neutropenia was an event of agranulocytosis received in the post-marketing period. The MAH believed that agranulocytosis represents a rare and idiosyncratic effect of pirfenidone administration. There is no pattern of increasing neutropenia with continuing administration of pirfenidone and all the cases identified in controlled clinical trials were significantly confounded. Consequently, the MAH believes that the data do not support listing neutropenia as an ADR in the SmPC.

Table 1: Patients in CAPACITY with Grade 2 or Higher Neutropenia

Patient ID	Neutropenia Max Grade	Pirfenidone dose	When occurred (study week)	Confounders/comments
PIPF-004-11025015	**3**	2403mg/day	4	No significant conmeds, no significant medical history; isolated finding at week 4. Pt continued on

				pirfenidone a further ~ 1.75 years without recurrence of neutropenia.
PIPF-004-10054135[1]	**2**	1197mg/day	4, 12, 72, 84	No significant conmeds, past prostate and testicular cancer. This patient had other associated AEs while in PIPF-004 i.e., macrocytic anemia, thrombocytopenia concurrent with the neutropenia (likely a bone marrow issue). Which 'resolved' end of PIPF-004. In PIPF-012 patient commenced lenolidamide for myeloproliferative disease (see Table 2)
PIPF-006-15096272[2]	**2**	2403mg/day	Baseline, 2, 6, 12, 36, 60, 72	Neutropenia at baseline and improved despite continuation of pirfenidone.

BLUE = Grade 1, GREEN = Grade 2, RED = Grade 3

1 This patient is counted twice because of roll over from CAPACITY to PIPF-012

2 Patient should be discounted because neutropenia existed at baseline and improved while on pirfenidone.

Table 2: Patients in PIPF-012 with Grade 2 or Higher Neutropenia

Patient ID	Neutropenia Max Grade	When occurred (study week)	Confounders/Comments
PIPF-004-10054135[1]	2	36, 48, 60, 84, 96, 132, 144, 156, 180	Lenalidomide treatment for myeloproliferative disease, Hx of prostate and testicular cancer. Possible past chemotherapy.
PIPF-004-23065124	2	48	Lung cancer, chemotherapy (carboplatin, etopside), radiation therapy, prednisone use for IPF worsening
PIPF-006-15136008	3	144	Adenocarcinoma of cecum, chemotherapy (5-FU, oxaliplatin)
PIPF-006-15266263	3	2, 6, 12, 24, 36, 48, 60, 84, 96, 108, 120, 132, 144, 156, 168, 180	Crohn's disease
PIPF-006-15096272[2]	2	Baseline, 2, 36, 48, 60	Lung cancer, chemotherapy (avastin, carboplatin, paclitaxol), bone marrow biopsy for unknown myelodysplasia prior to pirfenidone treatment

BLUE = Grade 1, GREEN = Grade 2, RED = Grade 3

1 This patient is presented twice because of roll over from CAPACITY to PIPF-012

2 Patient should be discounted because neutropenia existed at baseline and improved while on pirfenidone.

The frequency of neutropenia in clinical studies was 21/848 patients exposed to pirfenidone, which is approximately 2.5%. The MAH maintains this frequency of neutropenia was consistent with the

background rate of neutropenia in a healthy population of this age but cited studies which gave a range of WBC and ANC values in healthy American-born women of African descent and European descent, and women from Barbados/Trinidad-Tobago; Dominican Republic, Haiti, and Jamaica, or in the various ethnicities in the US population. It is therefore not clear which ANC values the MAH considers are comparable to those seen in the pirfendione clinical development programme or whether similar patients to those described in these publications were exposed in the clinical trials for pirfenidone (which were conducted in several countries).

Post Marketing Data

The MAH presented data collection programs such as the Named Patient Program (NPP), PIPF-025 post-authorization safety study (PASSORT), and the post-marketing surveillance program (SMPS) in Japan from Shionogi & Co. Ltd. to be taken into account for calculation of patient exposure numbers. In these programs, an approximate 1800 subjects from NPP, 500 from PASSPORT, and 1400 from the SPMS program for a total of 3700 additional subjects can be added to the total program subjects. This would yield a total exposure of 4875 subjects (1175 clinical + 3700 solicited). This would make the frequency less than 1:1000 and be appropriate for the rare category (~2 agranulocytosis/4875 subjects). In addition, for pirfenidone, a preponderance of the patient event reporting is coming from solicited reporting with the cumulative adverse reaction load being 2054 (66.8%) ADRs coming from solicited reporting (see PSUR 5 Section 7.3 - Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources). This suggests that more intensive surveillance for pirfenidone (Esbriet) is occurring and that a typical “worst value estimate” using the 3X estimation from the SmPC guideline would be too high. Following request to the MAH to justify the chosen frequency, the MAH proposed continuing to use “rare” as the frequency for agranulocytosis in 4.8 for the following reasons which were endorsed by the CHMP; MAH contends solicited data collection programs such as the Named Patient Program (NPP), PIPF-025 post-authorization safety study (PASSORT), and the post-marketing surveillance program (SMPS) in Japan from Shionogi & Co. Ltd. should also be taken into account for calculation of patient exposure numbers. In these programs, an approximate 1800 subjects from NPP, 500 from PASSPORT, and 1400 from the SPMS program for a total of 3700 additional subjects can be added to the total program subjects. This would yield a total exposure of 4875 subjects (1175 clinical + 3700 solicited). This would make the frequency less than 1:1000 and be appropriate for the rare category (~2 agranulocytosis/4875 subjects). In addition, for pirfenidone, a preponderance of the patient event reporting is coming from solicited reporting with the cumulative adverse reaction load being 2054 (66.8%) ADRs coming from solicited reporting (see PSUR 5 Section 7.3 - Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources). This suggests that more intensive surveillance for pirfenidone (Esbriet) is occurring and that a typical “worst value estimate” using the 3X estimation from the SmPC guideline would be too high. Therefore, the MAH proposes continuing to use “rare” as the frequency for agranulocytosis.

In the post-market period, only two events of neutropenia have been reported in the pirfenidone safety database (MCN 201111IM002188 and 200708IM000319). In the first case from Shionogi & Co in Japan, the patient recovered from neutropenia while remaining on Pirespa (pirfenidone). In the second case, the patient was receiving pirfenidone for treatment of neurofibromatosis in an investigator sponsored clinical trial. Maximum grade in that case was grade 2. There have been five events of WBC decreased in the pirfenidone safety database (MCN 201306IM003639, 201107IM002026, 200906IM000271, 201001IM000925, 200912IM000837). Four of these events were from Pirespa reporting in the Shionogi Post Marketing Surveillance Program (SPMS) in Japan and were non-serious with only limited information available with the exception of MCN200906IM000271. The patient in that case has a complex history including diabetes, pneumonia, and use of hemoperfusion

treatment that may have contributed to the event. In all there is no evidence of a signal of neutropenia in the post-marketing setting.

Late-breaking information

The MAH stated that a case of potential anaphylaxis/angioedema was reported after the close of the data collection period of this PSUR. In this case, a 55-year-old female patient with end stage IPF in the United Kingdom started receiving pirfenidone in August 2013 (MCN 201308IM004069). Concomitant medication included hormone replacement therapy and N-acetylcysteine. Approximately two weeks after Esbriet was started, Esbriet dosage was increased to 534 mg three times daily (1602 mg daily). The patient began experiencing symptoms (not detailed) that prompted discontinuation of pirfenidone. Three days later, the patient woke up with facial swelling, lip and posterior tongue swelling. The patient also had shortness of breath, right sided chest pain, nausea, and vomiting. Symptoms were partially relieved by chlorpheniramine given at home. The patient went to the hospital and was hypotensive (blood pressure 60-70 systolic) and was further treated with intravenous hydrocortisone and intramuscular adrenaline x2. Swelling improved further but was not completely resolved. She became progressively hypoxic and short of breath and was admitted to the intensive care unit. Approximately one month after starting Esbriet and ten days after the report of anaphylaxis, the patient died. The cause of death was thought to be acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF). No autopsy or lung biopsy was performed. The reporter considered anaphylaxis unlikely. According to the reporter, angioedema was the diagnosis. An analysis of the safety database to review these events is ongoing.

This case was reported directly to the MHRA's Yellow Card database and in the narrative it is stated that the diagnosis of angioedema was a diagnosis of exclusion, confirmed by low levels of complement component 3 (C3) 0.46 g/L (normal range: 0.88-2) and component 4 (C4) 0.08 g/L (normal range: 0.16-0.47).

The cumulative summary tabulations capture 1 serious case of anaphylaxis reported during the review period (bringing the cumulative total to 2 cases) and 1 serious case of angioedema reported during this period of review but no further details or discussion of these cases is provided. It is not known whether the late-breaking information described above is included amongst these reports.

One additional case of anaphylactic reaction has been reported directly the MHRA through the Yellow card database, describing events which occurred after the submission date of this PSUR. This concerned a 69–year-old male patient who (at the end of October 2013) took 1 dose in the morning and a further dose at lunchtime. The patient's tongue started to tingle, by 4pm their tongue was swollen, and at 10pm there was significant deterioration in breathing. The patient was admitted to the Intensive Care Unit to manage anaphylaxis. Treatment was with adrenaline and steroids as per protocol. There was 48 hours hospital admission. The drug was withdrawn and the patient recovered.

In light of the number of cases of anaphylaxis/anaphylactic reactions reported to date and the late-breaking case of angioedema described above, the MAH should provide its analysis of the safety database to review these events.

The MAH has not explained how the 50 cases initially identified using the MedDRA SMQs of anaphylaxis, angioedema and hypersensitivity were narrowed down to 13 cases and it is unclear why the other 37 cases were not considered to represent anaphylaxis, angioedema or hypersensitivity. This should be clarified in the next PSUR and further details provided of the other 37 cases which were excluded from this review.

In the review, the MAH describes 14 cases of angioedema (two initially reported as anaphylaxis and 1 originally reported as SJS), all but one of which were considered serious, 7 of which involved positive

dechallenge and 2 of which involved positive rechallenge. The case of anaphylaxis with fatal outcome and the case initially reported as SJS were reviewed by Dr Jonathan Wilkin and his assessment of these cases as being more likely to be angioedema is endorsed. It would appear that none of the 14 cases reported to date are consistent with symptoms of anaphylactic reaction.

The MAH's proposal to include 'angioedema' in product information as an unwanted ADR is therefore endorsed. However, two cases of positive rechallenge (and no cases of negative rechallenge) were reported and angioedema is potentially very serious in any patient but could have particularly severe consequences in patients with IPF, in whom the airway is already compromised. One case initially reported as anaphylaxis was considered to have symptoms more consistent with angioedema. This patient died, seemingly from progression of IPF, but the MAH acknowledges that the role of angioedema in this case also needs to be considered. In light of this, it is therefore not considered appropriate that patients who have previously experienced angioedema should be treated with pirfenidone given the already higher risk of respiratory complications in these patents. It would therefore be appropriate to contraindicate use of pirfenidone in patients who have previously experienced angioedema with pirfenidone treatment. The proposed warning of 'should not be used' in section 4.4 be therefore be upgraded to a contraindication in section 4.3.

It is agreed that angioedema should be considered an important identified risk and the RMP updated as such; the questionnaire provided with the MAH's response is acceptable and should be captured as a routine Pharmacovigilance measure for the identified risk of angioedema.

2.2.3. Discussion

The MAH's proposal to include 'agranulocytosis' in section 4.8 of the SmPC following a spontaneous case report received in June 2013 is endorsed by the CHMP with a frequency category of 'rare'. The MAH also proposed to update the Patient Leaflet section 4 in line with how warnings on the risk of agranulocytosis are usually expressed in the Patient Leaflet.

In both cases of agranulocytosis, the time to onset was approximately 2 months (with a third case initially reported as 'agranulocytosis' but actually reporting a less severe instance of decreased neutrophil count having a time to onset of approximately 4 weeks). In all cases, patients were symptomatic, reporting symptoms of fever or pyrexia. This highlights the importance of describing the symptoms of infection in the Patient Leaflet. At present, therefore, there does not appear to be justification for inclusion of any warning or precaution for use in section 4.4 of the SmPC to advise prescribers that blood tests should be performed before and during treatment to monitor the risk of haemopoietic reactions. However, it was considered to add in section 4 of the PL information to perform a blood test if a patient get signs of an infection such as a sore throat, fever, mouth ulcers or flu-like symptoms to check if patients symptoms are related to patient's medicine.

The MAH has provided after request for supplementary information more substantial and satisfactory discussion of the cases of neutropenia reported to date in association with use of pirfenidone. In particularly, the MAH has clarified that figures 1 and 2 may include the same patient include multiple times, and therefore the frequency of neutropenia is lower than may appear from these figures. The MAH has additionally clarified that the reporting pattern on neutropenia is not consistent with that of other cytotoxic drugs, where an increased frequency and severity could be expected with extended use at higher doses.

The MAH has provided a discussion of cases reported in CAPACITY and PIPF-012 and it is clear that confounding factors which could have accounted for the course of events are present in virtually all of these cases. The cases reported spontaneously are also largely confounded and it is therefore agreed in light of the additional information now provided that 'neutropenia' need not be included in the

SmPC as an ADR at this time.

In its response on the proposals for product labelling that MAH stated that respiratory infection occurs more frequently in idiopathic pulmonary fibrosis and in elderly patients which make up a great majority of the patients treated with Esbriet. It is agreed that it may be difficult to distinguish between the symptoms suggestive of agranulocytosis (fever, sore throat, mouth ulcers) and those of respiratory infections. Therefore, mandating blood tests when such symptoms are reported could impose an unnecessary burden on healthcare professionals and patients given that events of agranulocytosis are rare. Nevertheless, this is an area which the MAH should keep under careful review. If further blood dyscrasias become listed side-effects for pirfenidone, the need to include a precaution for use to perform a full blood count in cases of unexplained infection that are clearly different to IPF-related respiratory infections should be considered.

The MAH agreed to update the Esbriet SmPC Section 4.4 to add a reference to a small number of patients experiencing angioedema. Additionally, the MAH updated Section 4.8 to add language stating that angioedema have been observed in post-marketing safety surveillance. . Corresponding sections of the Patient Leaflet was revised. The frequency of this event is approximately 12 out of 12,000 exposed patients (1/1000) qualifying this event as uncommon and endorsed by the PRAC. This includes a contraindication in patients who have previously experienced angioedema related to pirfenidone. The MAH's selection of frequency is appropriate given that no cases of angioedema were reported in the clinical development programme in which 1175 patients were exposed to pirfenidone. The upper limit of the 95% confidence interval is therefore 1/392 or less and the frequency category should be "uncommon", based on worst value of the point estimate.

2.3. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

In the SmPC:

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- history of angioedema with pirfenidone (see section 4.4),
- concomitant use of fluvoxamine (see section 4.5),
- 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

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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 use of Esbriet in the post-marketing setting. Therefore, patients who develop signs or symptoms of angioedema following administration of 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).

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4.8 Undesirable effects

The safety of Esbriet has been evaluated in clinical studies including 1345 healthy volunteers and patients.

The most commonly reported (≥10%) adverse reactions during clinical study experience with Esbriet at a dose of 2403 mg/day compared to placebo, respectively, were nausea (32.8% versus 13.3%), rash (28.7% versus 8.6%), fatigue (22.3% versus 13.3%), diarrhoea (21.7% versus 13.5%), dyspepsia (16.8% versus 5.5%), and photosensitivity reaction (12.2% versus 1.7%).

Serious adverse reactions were recorded at similar frequencies among patients treated with 2403 mg/day of Esbriet and placebo in clinical studies.

Table 3 shows the adverse reactions reported at a frequency of ≥2% in 345 patients receiving Esbriet at the recommended dose of 2403 mg/day in two pivotal Phase 3 studies. Adverse reactions from post-marketing experience are also listed in Table 3. Adverse reactions are listed by System Organ Class (SOC) and within each frequency grouping [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)] the adverse reactions are presented in order of decreasing seriousness.

Table 3 Adverse reactions by SOC and MedDRA frequency	
Infections and infestations	
Common:	Upper respiratory tract infection; urinary tract infection
Blood and lymphatic system disorders	
Rare:	Agranulocytosis[1]
Immune system disorders	
Uncommon:	Angioedema[1]
Metabolism and nutrition disorders	
Common:	Weight decreased; anorexia; decreased appetite
Psychiatric disorders	
Common:	Insomnia
Nervous system disorders	
Common:	Dizziness; headache; somnolence; dysgeusia
Vascular disorders	
Common:	Hot flush
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea; cough; productive cough
Gastrointestinal disorders	
Very Common:	Dyspepsia; nausea; diarrhoea
Common:	Gastroesophageal reflux disease; vomiting; abdominal distension; abdominal discomfort; abdominal pain; abdominal pain upper; stomach discomfort; gastritis; constipation; flatulence
Hepatobiliary disorders	
Common:	ALT increased; AST increased; gamma glutamyl transferase increased
Rare:	Total serum bilirubin increased in combination with increases of ALT and AST[1]

Table 3 Adverse reactions by SOC and MedDRA frequency	
Skin and subcutaneous tissue disorders	
Very Common:	Photosensitivity reaction; rash
Common:	Pruritus; erythema; dry skin; rash erythematous; rash macular; rash pruritic
Musculoskeletal and connective tissue disorders	
Common:	Myalgia; arthralgia
General disorders and administration site conditions	
Very Common:	Fatigue
Common:	Asthenia; non-cardiac chest pain
Injury poisoning and procedural complications	
Common:	Sunburn

1. Identified through post-marketing surveillance

In the PL:

2. What you need to know before you take Esbriet

Do not take Esbriet

- if you are allergic to pirfenidone or any of the other ingredients of this medicine (listed in section 6)
- if you have previously experienced angioedema with pirfenidone, including symptoms such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing
- if you are taking a medicine called fluvoxamine (used to treat depression and obsessive compulsive disorder (OCD))
- if you have severe or end stage liver disease
- if you have severe or end stage kidney disease requiring dialysis.

If any of the above affects you, do not take Esbriet. If you are unsure ask your doctor or pharmacist.

4. Possible side effects

Stop taking Esbriet and tell your doctor immediately

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- If you get signs of an infection such as a sore throat, fever, mouth ulcers or flu-like symptoms. You may need to have a blood test to check if your symptoms are related to your medicine.

...

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 1,000 people):

- blood tests may show decrease in white blood cells

3. Overall conclusion and impact on the benefit/risk balance

The safety concerns remain in accordance with the known safety profile of pirfenidone although a further case of agranulocytosis reported in a patient in Canada has led the MAH to update product information; blood dyscrasias are already included in the RMP as an important potential risk.

The MAH provided a review of angioedema/anaphylaxis which described 14 cases of angioedema (two initially reported as anaphylaxis and 1 initially reported as Stevens-Johnson Syndrome, with all 3 considered more likely to be cases of angioedema). All but one of these 14 cases was considered serious, 7 cases involved positive dechallenge and 2 cases involved positive rechallenge. On the basis of this review the MAH proposes to update product information to include 'angioedema' as an uncommonly reported ADR (with consequential changes to the Patient Leaflet). In view of the potentially life-threatening nature of these events and the available data regarding reports of angioedema associated with use of pirfenidone, the PRAC agreed that changes to the product information were warranted. Update following parallel PRAC outcome PSUR 5 assessment of SmPC section 4.3 of the SmPC to include a contraindication in patients who have previously experienced angioedema with pirfenidone, update of section 4.4 to add a warning on the risk of angioedema and the need for patients who develop signs or symptoms of angioedema following administration of pirfenidone to discontinue treatment and update of section 4.8 of the SmPC to add 'angioedema' with a frequency 'uncommon'.

The MAH has submitted an update of the RMP on the 7th May 2014 to include 'angioedema' as an important identified risk and the proposed follow-up questionnaires should be captured as a routine Pharmacovigilance measure to address this risk. The updates to product information on the risk of angioedema will also need to be reflected in the section on risk minimisation and the RMP summary should be updated accordingly. The MAH will continue to monitor all blood dyscrasias in the RMP.

The benefit risk balance of Esbriet in the approved indications remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of section 4.8 of the SmPC to include 'agranulocytosis' as a rare event as a result of post marketing surveillance. Update of section 4.3, 4.4 and 4.8 of the SmPC with information on the risk of angioedema.

The Package Leaflet was proposed to be updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.