Esbriet

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IAIN/0081	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/03/2024		SmPC and PL	
IA/0080	A.7 - Administrative change - Deletion of manufacturing sites	15/06/2023	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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II/0074	Extension of indication to include treatment of 'advanced' idiopathic pulmonary fibrosis (IPF) by the deletion of the current qualifier 'mild to moderate', based on the results from Study MA29957; this is a 52-week Phase IIb, multicentre, randomised, double-blind, placebo-controlled clinical trial in IPF patients with advanced lung function impairment (DLco < 40% of predicted) and at high risk of grade 3 pulmonary hypertension, and additional analyses performed on the original pivotal trials for pirfenidone in IPF. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. In addition, the MAH took the opportunity to include information in section 4.4 of the SmPC related to the content of sodium per Esbriet capsule and tablet. The Package Leaflet is updated in accordance. Version 12.1 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/02/2023	24/03/2023	SmPC and PL	Please refer to Scientific Discussion 'Esbriet-H-C-2154-II-0074'.
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2023		PL	
IA/0078	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	05/08/2022	24/03/2023	SmPC, Labelling and PL	
N/0077	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/06/2022	24/03/2023	Labelling and	

				PL	
IA/0076	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	08/03/2022	n/a		
IA/0075	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	25/02/2022	n/a		
PSUSA/2435/202102	Periodic Safety Update EU Single assessment - pirfenidone	14/10/2021	09/12/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2435/202102.
IA/0073	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	07/07/2021	n/a		
II/0070	Update of section 4.8 of the SmPC to revise the MeDRA frequency categories for some adverse drug reactions (ADR) and to combine the ADR 'anorexia' with the preferred term 'decreased appetite' based on a safety update report previously submitted in variation EMEA/H/C/2154/II/0021. The package leaflet is updated accordingly. Minor formatting changes were introduced in Annex II, IIIA and IIIB in the list of local representatives. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	10/06/2021	09/12/2021	SmPC, Annex II, Labelling and PL	

	data				
IA/0071	A.7 - Administrative change - Deletion of manufacturing sites	12/03/2021	n/a		
II/0066/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on drug-induced liver injury (DILI) subsequent to the latest PSUSA (EMEA/H/C/PSUSA/00002435/201902) and post-authorisation measure (EMEA/H/C/2154/LEG/015). The annex II and package leaflet (PL) are updated accordingly. The RMP version 10.2 has also been updated. In addition, the MAH took the opportunity to add in the PL information about sodium content in line with excipients guideline (EMA/CHMP/302620/2017) and to correct formatting, punctuation and spelling mistakes in the product information. Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on hyponatraemia and to add hyponatraemia with a frequency 'uncommon' to the list adverse reactions subsequent to the latest PSUSA (EMEA/H/C/PSUSA/00002435/201902) and post-authorisation measure (EMEA/H/C/2154/LEG/015). The PL is updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the	01/10/2020	16/11/2020	SmPC, Annex II and PL	Drug-induced liver injury: Elevated transaminases have been commonly reported in patients treated with Esbriet. 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. Liver function tests (ALT, AST and bilirubin) should be performed prior to the initiation of treatment with Esbriet, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter. In addition, 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. In the event of significant elevation of liver aminotransferases or clinical signs and symptoms of liver injury, the dose of Esbriet should be adjusted or treatment discontinued according to the guidelines listed below. For patients with confirmed elevations in ALT, AST or bilirubin during treatment, the following dose adjustments may be necessary. Discontinuation of other medicines associated with liver toxicity should be considered. Hyponatraemia has been reported in patients treated with Esbriet. As the symptoms of hyponatraemia may be subtle and masked by the presence of concomitant morbidities, regular monitoring of the relevant laboratory parameters is

	assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				recommended, especially in the presence of evocative signs and symptoms such as nausea, headache or dizziness. For more information, please refer to the Summary of Product Characteristics.
PSUSA/2435/ 202002	Periodic Safety Update EU Single assessment - pirfenidone	01/10/2020	n/a		PRAC Recommendation - maintenance
IA/0068/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	04/06/2020	n/a		

	Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IB/0065	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	16/01/2020	n/a		
IB/0064/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	09/01/2020	16/11/2020	SmPC	
IB/0063/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new	19/12/2019	n/a		

	specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
PSUSA/2435/ 201902	Periodic Safety Update EU Single assessment - pirfenidone	19/09/2019	11/11/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2435/201902.
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/03/2019	09/04/2019	Labelling and PL	
IA/0061/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	12/03/2019	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites				
IB/0059	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	19/12/2018	n/a		
IB/0058/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.f.1.e - Stability of FP - Change to an approved stability protocol	04/10/2018	n/a		
PSUSA/2435/ 201802	Periodic Safety Update EU Single assessment - pirfenidone	06/09/2018	n/a		PRAC Recommendation - maintenance
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	09/04/2019	PL	
IG/0949/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting	04/06/2018	n/a		

	material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IB/0051	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	07/05/2018	n/a		
IAIN/0053/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	17/04/2018	09/04/2019	SmPC, Labelling and PL	
T/0052	Transfer of Marketing Authorisation	16/03/2018	04/04/2018	SmPC, Labelling and PL	
SW/0054	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0011	14/12/2017	08/02/2018	Annex II	The prospective observational registry submitted by the MAH complies with their obligation to conduct a prospective observational registry to evaluate long-term safety in a real-world setting, as imposed during the marketing authorisation of Esbriet (pirfenidone) procedure EMEA/H/C/002154. Therefore, in view of available data

					regarding the PASS final study report, the PRAC considered that changes to the conditions of the marketing authorisation were warranted.
IG/0887	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	29/01/2018	n/a		
IA/0049	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	18/12/2017	n/a		
II/0043	Update of sections 4.2 and 5.2 of the SmPC in order to update dosing recommendations and pharmacokinetic information for patients with renal impairment based on the totality of data from clinical studies; the Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/10/2017	08/12/2017	SmPC and PL	No dose adjustment is necessary in patients with mild renal impairment. Esbriet should be used with caution in patients with moderate (CrCl 30-50 ml/min) renal impairment. Esbriet therapy should not be used in patients with severe renal impairment (CrCl <30 ml/min) or end stage renal disease requiring dialysis. The use of pirfenidone is contraindicated in patients with severe renal impairment (CrCl <30ml/min) or end stage renal disease requiring dialysis. Approximately 70–80% of pirfenidone is metabolised via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1. In vitro data indicate some pharmacologically relevant activity of the major metabolite (5 carboxy-pirfenidone) at concentrations in excess of peak plasma concentrations in IPF patients. This may become clinically relevant in patients with moderate renal impairment where plasma exposure to 5 carboxy-pirfenidone is increased. The mean exposure to 5 carboxy-pirfenidone was significantly higher in the

					moderate and severe renal impairment groups than in the group with normal renal function.
PSUSA/2435/ 201702	Periodic Safety Update EU Single assessment - pirfenidone	28/09/2017	n/a		PRAC Recommendation - maintenance
IA/0047	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	18/08/2017	n/a		
IB/0046/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished	26/06/2017	08/12/2017	SmPC, Labelling and PL	

	product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IA/0044/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	24/05/2017	n/a		
X/0035/G	This was an application for a group of variations. Extension application to introduce a new pharmaceutical form associated with 3 new strengths	23/02/2017	24/04/2017	SmPC, Labelling and PL	

	(267mg, 534mg and 801mg film-coated tablets). In addition, the following manufacturing sites are also introduced for the currently approved 267mg hard capsules presentations (EU/1/11/667/001-003): B.I.b.1.f - To add F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 Basel, Switzerland, as an alternative site responsible for quality control of the active substance B.I.b.1.f - To add Synlab Umweltinstitut GmbH, St. Peter-Strasse 25, 4020 Linz, Austria, as an alternative site responsible for quality control of the active substance Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
IB/0042	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other	11/04/2017	n/a		

	variation				
IB/0041	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	08/02/2017	n/a		
II/0039	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	15/12/2016	n/a		
IB/0040/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	18/10/2016	n/a		

PSUSA/2435/201602	Periodic Safety Update EU Single assessment - pirfenidone	29/09/2016	n/a		PRAC Recommendation - maintenance
IA/0038/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	01/08/2016	24/04/2017	SmPC and PL	
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/05/2016	24/04/2017	Labelling	
IG/0667/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved	08/04/2016	n/a		

	manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IB/0033/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	14/01/2016	n/a		
IA/0032/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or	16/10/2015	n/a		

	manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
PSUSA/2435/201502	Periodic Safety Update EU Single assessment - pirfenidone	10/09/2015	n/a		PRAC Recommendation - maintenance
R/0029	Renewal of the marketing authorisation.	23/07/2015	08/09/2015	SmPC, Annex II, Labelling and PL	Based on the review of available information, the CHMP is of the opinion that the quality, safety and efficacy of Esbriet continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be favourable. The product information has been updated to bring it in line with new QRD template. The CHMP recommends that the renewal be granted with unlimited validity.
IAIN/0031	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	30/07/2015	n/a		
IAIN/0028/G	This was an application for a group of variations. B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings B.II.b.2.c.1 - Change to importer, batch release	07/05/2015	08/09/2015	SmPC, Annex II and PL	

	arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
PSUSA/2435/201408	Periodic Safety Update EU Single assessment - pirfenidone	12/03/2015	n/a		PRAC Recommendation - maintenance
T/0027	Transfer of Marketing Authorisation	26/01/2015	12/02/2015	SmPC, Labelling and PL	Transfer of Marketing Authorisation from InterMune UK Ltd. to Roche Registration Limited.
IAIN/0026	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	08/01/2015	n/a		
IB/0024/G	This was an application for a group of variations. B.II.e.5.z - Change in pack size of the finished product - Other variation B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement	18/12/2014	12/02/2015	SmPC, Labelling and PL	

	B.II.e.5.z - Change in pack size of the finished product - Other variation				
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/12/2014	12/02/2015	PL	
II/0021	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	12/02/2015	SmPC and PL	In this variation sections 4.8 and 5.1 of the SmPC have been updated with safety and efficacy information based on the results of three studies ASCEND/PIPF-016, PIPF-012 and PIPF-002. The efficacy data provided from study PIPF-016 (Phase 3 randomized, double-blind, placebo-controlled), as well as the new pooling of the 52 week efficacy data have further demonstrated the efficacy of pirfenidone in IPF, especially with regards rate of FVC decline, 6MWT performance and mortality data. In addition, the safety update from the ongoing open label studies (PIPF-002 and 012) as well as the safety data from PIPF-016 have allowed the company to further refine the adverse event profile over long term use.
IAIN/0022/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) in the safety database and/or major contractual arrangements for the fulfilment of PhV obligations, and/or change of the site undergoing PhV activities C.I.9.c - Changes to an existing pharmacovigilance	29/09/2014	n/a		

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the PhV system				
PSUV/0020	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
II/0016	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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	27/06/2014	SmPC and PL	Update of Section 4.8 of the SmPC to add "agranulocytosis" following a spontaneous case report received by the MAH following post-marketing data. 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'.
PSUV/0018	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
II/0014/G	This was an application for a group of variations. B.I.a.1.g - to add an alternative manufacturer of the active substance (pirfenidone) B.I.a.1.f - to add an alternative site for microbiological testing of pirfenidone manufactured at the alternative site B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is	20/02/2014	n/a		

	not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
IAIN/0019/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) in the safety database and/or major contractual arrangements for the fulfilment of PhV obligations, and/or change of the site undergoing PhV activities C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the PhV system	09/01/2014	n/a		
PSUV/0017	Periodic Safety Update	24/10/2013	17/12/2013	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0017.
IB/0013/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-	08/11/2013	n/a		

	release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IA/0015	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	04/10/2013	n/a		
IAIN/0012/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) in the safety database and/or major contractual arrangements for the fulfilment of PhV obligations, and/or change of the site undergoing PhV activities C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s)	21/08/2013	17/12/2013	SmPC, Annex II, Labelling and PL	

	to the DDPS that does not impact on the operation of the PhV system				
IB/0011/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	25/07/2013	17/12/2013	SmPC and PL	
IB/0010	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	14/06/2013	n/a		
II/0008	Update of sections 4.5 and 5.2 of the SmPC with results of the ciprofloxacin DDI study (PIPF-017) to reflect the potential for drug interactions with CYP1A2 inhibitors, including a recommendation for caution when Esbriet is used in patients treated with moderate or strong and selective inhibitors of CYP1A2. Additionally, update of the PI with minor editorial changes and in accordance with the latest QRD template and update of the PL to update the information regarding several local representatives. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article	25/04/2013	17/12/2013	SmPC, Annex II, Labelling and PL	A number of in vitro-in vivo extrapolations (IVIVE) allowed for the modelling of potential changes in substrate drug AUC values secondary to drug-drug interaction studies (DDI) and indicate that strong and selective inhibitors of CYP1A2 have the potential to increase the exposure to pirfenidone by approximately 2 to 4-fold. Esbriet should be used with caution in patients treated with moderate or strong and selective inhibitors of CYP1A2. If concomitant use of Esbriet with a strong and selective inhibitor of CYP1A2 cannot be avoided the dose of Esbriet should be reduced and patients should be closely monitored for emergence of adverse reactions associated with Esbriet therapy. The treatment should be discontinued if necessary.

	45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				
IA/0009/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	09/04/2013	n/a		
IAIN/0007/G	This was an application for a group of variations. B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a	18/06/2012	29/10/2012	Annex II and PL	

	manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a				

	starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer				
IAIN/0006/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	19/01/2012	02/03/2012	SmPC, Labelling and PL	
N/0005	Inclusion of the list of local representatives in the Package Leaflet. The MAH also took the opportunity	01/12/2011	02/03/2012	Labelling and PL	

	to make minor linguistic changes to the Danish, Finnish, Norwegian, Icelandic and Swedish product information. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IA/0004/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	09/09/2011	n/a		
IA/0003	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	05/08/2011	05/08/2011	SmPC, Labelling and PL	
IA/0002/G	This was an application for a group of variations.	04/05/2011	n/a		

	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0001	A.1 - Administrative change - Change in the name and/or address of the MAH	20/04/2011	n/a	SmPC, Labelling and PL	