22 April 2022
EMA/584774/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pirfenidone AET

International non-proprietary name: pirfenidone

Procedure No. EMEA/H/C/005873/0000

Note

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

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List of abbreviations

AS	Active Substance
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CQAs	critical quality attributes
DoE	Design of Experiments
DS	Drug Substance
DSM	Drug Product Manufacturer
DP	Drug Product
DPM	Drug Product Manufacturer
DoE	Design of Experiments
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EP/ Ph. Eur.	European Pharmacopoeia
FPS	Finished Product Specifications
GC	Gas Chromatography
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPA	Isopropyl alcohol
IPC	In-Process Control
IR	Infrared spectroscopy
KF	Karl Fischer titration
LDPE	Low Density Polyethylene
LOD	Loss on Drying
LOD	Limit of Detection
LOQ	Limit of Quantitation
NLT	Not Less Than
NMT	Not More Than
PCTFE	polychlorotrifluoroethylene
PDE	Permitted Daily Exposure

PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PP	Polypropylene
ppm	parts per million
PSD	Particle Size Distribution
PVC	polyvinylochloride
QC	quality control
QbD	Quality by Design
QTPP	Quality Target Product Profile
RH	relative humidity
RPM	Revolutions Per Minute
RSD	Relative Standard Deviation
USP/NF	United States Pharmacopoeia / National Formula
UV	Ultraviolet spectrometry
XRD	X Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Alfred E. Tiefenbacher (GmbH & Co. KG) submitted on 28 April 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Pirfenidone AET, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 February 2021.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Pirfenidone AET is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Esbriet instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Esbriet, 267 mg, hard capsules
- Marketing authorisation holder: Roche Registration GmbH, at the time of authorisation the MAH was InterMune Europe Ltd
- Date of authorisation: 28-02-2011
- Marketing authorisation granted by: Union
- Union Marketing authorisation number: EU/1/11/667

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Esbriet 267 mg, 534 mg, 801 mg, film-coated tablets
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 24-04-2017
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/11/667

Medicinal product which is or has been authorised in accordance with Union provisions in force and to

which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Esbriet 801 mg, film-coated tablets
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 24-04-2017
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/11/667
- Bioavailability study number: 18-VIN-0385

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: John Joseph Borg

The application was received by the EMA on	28 April 2021
The procedure started on	20 May 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 August 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 September 2021
The applicant submitted the responses to the CHMP consolidated List of	26 December 2021

Questions on	
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	31 January 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 February 2022
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	23 March 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 April 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Pirfenidone AET on	22 April 2022

2. Scientific discussion

2.1. Introduction

This centralised application concerns a generic application according to Article 10(1) of Directive 2001/83/EC for Pirfenidone AET 267mg, 534mg, 801mg film coated tablets containing the same active substance as the originator.

The reference medicinal product is Esbriet marketed by Roche Registration GmbH and first authorised in the European Union on 02 March 2011 as immediate release hard capsule containing 267 mg of pirfenidone. In 2017, via a line extension, a new pharmaceutical form associated with three new strengths (267mg, 534mg and 801 mg film-coated tablets) were introduced. They form part of a global marketing authorisation (EU/1/11/667). The applicant of Pirfenidone AET has applied only for one pharmaceutical form, the film coated tablet, with the three strengths (267 mg, 534 mg and 801 mg).

The mechanism of action of pirfenidone has not been fully established. However, existing data suggest that pirfenidone exerts both antifibrotic and anti-inflammatory properties in a variety of in vitro systems and animal models of pulmonary fibrosis (bleomycin- and transplant-induced fibrosis).

IPF is a chronic fibrotic and inflammatory pulmonary disease affected by the synthesis and release of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β) and pirfenidone has been shown to reduce the accumulation of inflammatory cells in response to various stimuli.

Pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth

factors such as, transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF).

The indication applied for Pirfenidone AET is the same as authorised for the reference medicinal product Esbriet:

Pirfenidone is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 267 mg, 534 mg or 801 mg of pirfenidone as active substance.

Other ingredients are:

tablet core: mannitol, croscarmellose sodium, povidone, microcrystalline cellulose, colloidal anhydrous silica, sodium stearyl fumarate;

film coat: polyvinyl alcohol part hydrolyzed (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), iron oxide yellow (E172) (in 267 mg tablets only), sunset yellow FCF aluminium lake (E110) (in 534 mg tablets only), iron oxide red (E172) and iron oxide black (E172) (in 801 mg tablets only).

The product is available in white opaque High-Density Polyethylene (HDPE) bottles with a child-resistant and tamper-evident polypropylene screw caps or in white opaque PVC/PE/PCTFE aluminium blisters, as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of pirfenidone is 5-methyl-1-phenylpyridin-2(1*H*)-one corresponding to the molecular formula $C_{12}H_{11}NO$. It has a relative molecular mass of 185.2 g/mol and the structure shown in Figure 1.

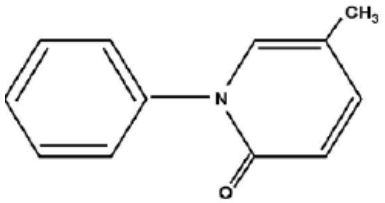

Figure 1: Active substance structure

Pirfenidone is white or pale yellow, not hygroscopic, crystalline powder. It is sparingly soluble in water, freely soluble in ethanol (96%), slightly soluble in heptane. There is only one polymorphic form of pirfenidone, designated as Form A. It was shown that no change in the polymorphic form occurs during finished product manufacturing and storage.

As there is a monograph of pirfenidone in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for pirfenidone which has been provided within the current Marketing Authorisation Application.

2.2.2.2. Manufacture, characterisation and process controls

The relevant information on the manufacture of pirfenidone has been assessed by the EDQM before issuing the CEP.

The CEP specifies that the active substance (AS) is packaged in a double polyethylene bags (outer black) placed in a polyethylene drum as approved by the European Directorate for the Quality of Medicines (EDQM) in relation to the Certificate of Suitability.

According to the CEP, no material of human or animal origin is used in the synthesis of the AS.

2.2.2.3. Specification(s)

The CEP confirms that the pirfenidone is suitably controlled by the Ph. Eur. monograph (no. 01/2016:2856).

The AS specification is based on the Ph. Eur. monograph and includes tests for description, solubility (Ph. Eur.), identification (IR, HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), related substances (HPLC and GC), assay (HPLC) and residual solvents (GC).

In addition, the following specifications parameters are set up by the finished product manufacturer: residual solvent benzene (GC) and particle size (laser diffraction). Most of the analytical methods are according to the Ph. Eur. Non-compendial methods have been adequately described and appropriately validated in accordance with the ICH Q2. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for three commercial scale batches of the AS tested by the finished product manufacturer were provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

No re-test period is defined in the CEP.

Stability data from seven commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Stability batches were tested for the following parameters: appearance, identification, loss on drying, assay and related substances. The analytical methods used for the stability testing were the same as for release and were stability indicating. Results for all tested parameters met the specification at all timepoints.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period without special storage conditions in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

Pirfenidone AET finished product is immediate release film-coated tablets containing 267 mg, 534 mg, or 801 mg of pirfenidone.

The 267 mg tablets are yellow coloured, oval shaped, biconvex film-coated tablets with approximate dimensions 13.2 x 6.4 mm debossed with "LP2" on one side and plain on other side.

The 534 mg tablets are orange coloured, oval shaped, biconvex film-coated tablets with approximate dimensions 16.1 x 8.1 mm, debossed with "LP5" on one side and plain on other side.

The 801 mg tablets are brown coloured, oval shaped, biconvex film-coated tablets with approximate dimensions 20.1 x 9.4 mm, debossed with "LP8" on one side and plain on other side.

The finished product has been developed to be a generic equivalent to the reference medicinal product Esbriet. Consequently, the objective was to prepare a film-coated tablet which is essentially similar to the reference medicinal product.

The different tablet strengths have the same shape (oval and biconvex). However, different strengths are distinguishable by the colour, size and debossing on the tablets.

The excipients used in the product are considered safe in the proposed concentrations. The differences from the reference product Esbriet are the presence of magnesium stearate in the tablet core of the reference products and the presence of sodium stearyl fumarate and mannitol in the generic products which are absent from Esbriet. The coating solution has an in-house specification, but its components also comply with pharmacopoeial monographs (Ph. Eur.). All colouring agents used comply to EU No. 231/2012.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The compatibility of the AS with excipients was investigated. Results did not indicate any incompatibility.

Polymorphic changes of the AS during tablet manufacturing as well as during storage were studied and were evaluated using XRD analysis. No changes were observed.

The AS particle size can theoretically affect the content uniformity, dissolution and other granular characteristics such as flowability. Since pirfenidone is a highly soluble substance (BCS Class 1) a specification limit was set based on the PSD range of the tested batches.

The development of the manufacturing process has been well described. A wet granulation process was selected due to the physicochemical properties of the AS. An initial risk assessment of the impact of formulation variables on the defined finished product critical quality attributes (CQAs) was performed. Based on the initial risk assessment, critical process parameters were studied through development and optimisation studies conducted on laboratory and industrial scale batches. The impact on all CQAs was considered low except for dissolution.

Design of Experiments (DoE) studies were carried out during formulation development to evaluate high risk formulation variables identified in the initial risk assessment. The levels of binder (povidone), disintegrant (croscarmellose sodium) and diluent (mannitol) on dissolution was studied. Design of Experiments (DoE) studies were also carried out to investigate the optimum range of process variables

and to understand the effect of these variables on drug product dissolution. The experimental design selected was the central composite design to screen the variables. No design space is requested by the applicant but based on the presented data, optimal quantities for excipients mannitol, povidone and croscarmellose sodium, and wet granulation conditions were established.

The development of the dissolution method has been sufficiently described. The choice of the QC dissolution medium was based on the solubility of the AS, the dose range of the finished product to ensure that sink conditions are met and PK properties of the AS. The discriminatory power of the method was sufficiently demonstrated.

The applicant has conducted one bioequivalence study (BE) (18-VIN-0385) which demonstrated that the test product is bioequivalent to the reference product comparing the highest strengths. It was confirmed that the formulation of the test product that has been used in the BE study is the same as that intended for marketing. *In vitro* dissolution results between the test and reference biobatches have been provided complementary to bioequivalence studies as per the Guideline on Investigation on Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. Dissolution profiles were shown similar in all tested pH media as required by the above guideline.

A biowaiver for the two lower strengths, 267 mg and 534 mg, of the finished product has been requested. The similarity of the dissolution profiles of the two lower strengths with the 801 mg bio-batch was confirmed in all tested pHs conditions. All other conditions for the strength biowaiver have been met as per the Guideline on Investigation on Bioequivalence. Based on the information provided, the biowaiver of the additional strengths is acceptable from a quality perspective.

The primary packaging is white opaque HDPE bottles with child-resistant and tamper-evident polypropylene screw caps, or white opaque PVC/PE/PCTFE aluminium blisters. The materials comply with Ph. Eur. and EC requirements. The child-resistant cap screws conform to BS EN ISO 8317:2015. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of 13 main steps: sifting, dry mixing, binder solution preparation, granulation, drying, sifting and sizing of granules, blending, sifting of extra-granular materials, pre-lubrication, lubrication, compression, film-coating, packaging. The process is considered to be a standard manufacturing process. The manufacturing process has been described in sufficient detail. Critical steps have been identified and presented in the dossier and the respective proposed in process controls are acceptable to control the process. The proposed holding times are acceptable based on the presented hold time study results. The container closure system for the bulk tablets has been described and is acceptable.

Major steps of the manufacturing process have been validated by a number of studies. In addition, the applicant will to perform the process validation on the first three batches of any further batch sizes of each strength of pirfenidone film-coated tablets. This is acceptable considering this is standard manufacturing process. Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.2.3.3. Product specification(s)

The finished product release and shelf life specifications, include appropriate tests for this kind of dosage form: description, (visual), identification of AS (HPLC, UV), identification of titanium dioxide

and iron oxide (chemical reaction), water content (KF), dissolution (Ph. Eur., HPLC), assay (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC) and microbiological quality (Ph. Eur.).

The proposed specifications limits comply with the general requirements of the Ph. Eur. and the ICH guidelines ICH Q6A and Q3B(R2) and considered batch and stability results. The dissolution limit has been revised during the procedure following a Major Objection raised by the CHMP. The revised limit is in line with the biobatch dissolution data provided as per the reflection paper on the dissolution specification for generic solid oral immediate release products (EMA/CHMP/CVMP/QWP/336031/2017).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities (Options 2b). The risk assessment was carried out in order to demonstrate the worst-case scenario based on a maximum daily intake of 2403 mg. Since the total elemental impurity level from all sources in the finished product is less than 30% of the PDE (control threshold) in the five commercial batches tested, it has been concluded that no additional controls are required in the finished product specification.

A risk evaluation on the presence of nitrosamine impurities in the finished product was provided in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk of possible presence of nitrosamine impurities in the active substance or the related finished product was identified. Therefore, no additional control measures are deemed necessary. The nitrosamines risk evaluation report is considered acceptable.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented. The finished product is released on the market based on the above release specifications through traditional finished product release testing.

Batch analysis data have been provided on three commercial scale batches for each strength manufactured by the proposed manufacturer. All the test results were within the proposed specification limits demonstrating the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from three commercial scale batches of each strength stored for up to 36 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The stability batches are identical to those proposed for marketing and were packed in both types of the primary packaging proposed for marketing. The proposed bracketing approach for post-approval stability studies is considered acceptable in line with ICH Q1D.

Samples were tested for appearance, water content, dissolution, related substances, assay and microbiological quality. The analytical procedures used are stability indicating. The analytical methods used were the same as for release and are stability indicating.

The results complied with the specifications and no significant changes have been observed.

According to the EMA "Q&A on Quality of medicines Part 2" if long term and accelerated stability studies are not showing signs of deterioration or any stability related indicators, in-use stability studies

do not need to be undertaken. Stability and stress studies do not indicate that the finished product is susceptible to deterioration in quality over time. Therefore, it is agreed that in-use stability studies do not need to be undertaken.

A photostability study was conducted in accordance with ICH Q1B on one commercial scale batch of each strength. The test results met the acceptance criteria and no significant degradation was observed. Dissolution results met the limits in place at the time However, for completeness, because the limits have been revised since then, the CHMP requested the applicant to perform a photostability study on one batch during commercialisation and to submit dissolution testing results to demonstrate compliance with the tightened dissolution specification limit (Recommendation).

Based on available stability data, the proposed shelf-life of 3 years without any special storage conditions, as stated in the SmPC (section 6.3 and 6.4) is acceptable.

2.2.3.5. Adventitious agents

No materials of human or animal origin are used in the manufacture of the finished product.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. A major objection that had been raised about the specification limit for dissolution testing of the finished product has been resolved by tightening the limits in line with existing guidance. All questions have been addressed and resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the benefit-risk balance of the product related to performing a photostability study on the finished product and testing the dissolution profile a during this photostability study. This is proposed as a recommendation for future quality development (see below).

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to perform photostability studies on one batch during commercialisation and to test for dissolution during this photostability study in line with revised dissolution specification limit.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No environmental risk assessment (ERA) studies were submitted. This was justified by the applicant as the introduction of Pirfenidone AET is considered unlikely to result in any significant increase in the combined sales volumes for all pirfenidone containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The applicant has not conducted any toxicological or pharmacological studies on Pirfenidone 267 mg, 534 mg, 801 mg film-coated tablet, since this medicinal product contains the same active substance in the same concentration as the originator Esbriet 267 mg, 534 mg, 801 mg film-coated tablet, and is intended to be substitutable.

It was therefore accepted that Pirfenidone AET 267 mg, 534 mg, 801 mg film-coated tablets do not present any increased risks to the environment than the reference product and that further ERA studies were not required, in line with the Guideline on environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2*).

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology was provided, and was considered adequate by the CHMP. It is agreed that no further non-clinical studies are required. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considered that the non-clinical overview is based on up-to-date and adequate scientific literature. There are no objections to the approval of Pirfenidone AET 267 mg, 534 mg, 801 mg film-coated tablets from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing pirfenidone. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fed conditions (study 18-VIN-0385). This study was the pivotal study for the assessment.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr **) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) in its current version is of particular relevance.

The applicant provided a clinical overview outlining the well-established clinical pharmacology, efficacy and safety of pirfenidone based on published literature. The SmPC is in line with the SmPC of the reference product.

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant has conducted one bioequivalence study using the highest strength: Pirfenidone AET 801mg film-coated tablet and requested a biowaiver for the lower strengths: Pirfenidone AET 267mg and 534mg film-coated tablets.

In accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**) this is acceptable for products having several dosage strengths, in case all of the following conditions are fulfilled:

a) The pharmaceutical products are manufactured by the same manufacturer and process: Condition fulfilled.

b) The qualitative composition of the different strengths is the same: Condition fulfilled.

c) The ratio between the amounts of active substance and excipients is the same: Condition fulfilled.

d) Similar dissolution profiles under identical conditions for the additional strength and the strength used in the bioequivalence study: Condition fulfilled.

Furthermore, dose linearity across all strengths must be demonstrated. Upon request by the CHMP, evidence of dose linearity across all strengths was provided and was considered acceptable.

In conclusion, all above-mentioned conditions were fulfilled for pirfenidone tablets to allow extrapolation of the results of the presented bioequivalence study on the 801 mg strength to 267 mg and 534 mg strengths.

Tabular overview of clinical studies

To support the application, the applicant has submitted one bioequivalence study (18-VIN-0385).

Study Identifier	Objectives of the study	Study design and Type of Control	Test product, Dosage Regimen Route of administration	Number of Subjects	Healthy Subjects or patients	Duration of treatment	Study Status, Type of Report
18-VIN-0385	To compare the extent of absorption of Pirfenidone Tablets 801mg and Esbriet 801mg Film-coated tablets (Pirfenidone) of Roche Registration GmbH, Germany in healthy, adult, male, human	An open label, balanced, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study in healthy adult human subjects under fed condition. Treatment controlled.	**Test product(T):** Pirfenidone Tablets 801 mg Route of administration: One tablet was administrated orally **Reference product (R):** Esbriet 801mg Film-coated tablets Route of administration: One	60 Subjects enrolled; 50 Subjects completed the study	Normal, healthy, adult, male, human subjects	Single-Dose	Completed; abbreviated

	subjects under fed condition as well as to monitor the safety and tolerability of the subjects.		tablet was administrated orally				

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 18-VIN-0385: An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Pirfenidone Tablets 801 mg and Esbriet 801 mg Film-coated tablets (Pirfenidone) of Roche Registration GmbH, Germany in healthy, adult, male, human subjects under fed condition.

Methods

- **Study design**

This was a randomised, balanced, open label, single dose, two period, two sequence, two treatment, crossover oral bioavailability study to establish comparative bioequivalence of pirfenidone tablets 801 mg and Esbriet (pirfenidone) 801 mg film coated tablets (MAH: Roche Registration GmbH Germany) in 60 healthy, adult male subjects under fed conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of pirfenidone 801mg.

The study was conducted in two periods and in each period; the subjects received either test or reference products randomly.

Subjects were housed in clinical facility to ensure 10.00 hours overnight fasting before schedule time of start of a high-fat, high calorie breakfast and continued to be housed in the facility till 24.00 hours post-dose blood sample collection in each period.

- **Test and reference products**

Pirfenidone AET 801mg film-coated tablets has been compared to Esbriet 801mg film-coated tablets manufactured by Roche Registration Ltd, UK.

- **Population(s) studied**

Healthy, willing, male volunteers of age between 18 and 45 (both inclusive) years with a Body Mass Index (18.50 to 30.00 kg/m2 (both inclusive)) with a minimum of 45 kg weight were selected on the basis of laboratory evaluations, medical history, clinical examination (including vital signs (sitting and standing blood pressure, oral temperature, radial pulse rate and respiratory rate), physical examination and systemic examination), Chest Xray (PA view) and ECG recordings during screening.

As per protocol, 60 healthy adult male subjects were enrolled in the study who complied with all the inclusion criteria and none of the exclusion criteria. The study started with 60 subjects and 50 completed the study.

10 subjects withdrew from the study for the following different reasons:

- 2 subjects reported adverse events after the dosing of period 01
- 1 subject was found positive in drug of abuse test during the admission of period 02
- 1 subject was found positive in alcohol breath test during the admission of period 02

- 3 subjects did not report to the facility during the admission of period 02
- 3 subjects reported adverse events after the dosing of period 02

- **Analytical methods**

The plasma samples of subjects were analysed using a validated analytical test method to determine the concentrations of pirfenidone in the samples of all analysed subjects. A detailed description of the operative procedures and the validation process were provided and deemed acceptable by the CHMP.

- **Pharmacokinetic variables**

The following pharmacokinetic parameters were calculated:

- Primary PK Parameters: C_{max} and AUC_{0-t}
- Secondary PK Parameters: $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, λ_z and AUC_%Extrap_obs

The pharmacokinetic variables were adequate for the study.

- **Statistical methods**

Statistical tests like ANOVA, least square means for test and reference formulations, difference between test and reference formulations, intrasubject variability and power were calculated for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for pirfenidone.

Geometric least square means of test and reference formulations, its ratio, 90% confidence interval for geometric least square mean ratio and two one-sided tests for 90% confidence interval limits were calculated for pharmacokinetic parameters C_{max} and AUC_{0-t} for pirfenidone.

A two one-sided test for equivalence was performed to determine whether or not the geometric least squares mean ratio of test to reference treatments for ln-transformed C_{max} and AUC_{0-t} lies within 80.00-125.00%. To be bioequivalent the 90% confidence intervals for the ratio of geometric least square mean ratios (T/R) of C_{max} and AUC_{0-t} for pirfenidone should lie within 80.00-125.00%.

Pharmacokinetic and statistical analyses were performed on 50 subjects.

The appropriate variables were measured, and statistical methodology was acceptable.

Results

The results of the study are summarised in Table 1 and Table 2.

Table 1. Pharmacokinetic parameters for pirfenidone 801mg (fed n=50) (non-transformed values)

Pharmacokinetic parameter	Test product (T)		Reference product (R)	
	Arithmetic mean	SD CV%	Arithmetic mean	SD CV%
$AUC_{(0-t)}$ (hr*ng/mL)	47691.165	17203.6459 36.07%	46326.604	16877.5801 36.43%
$AUC_{(0-\infty)}$ (hr*ng/mL)	48156.906	17468.9658 36.28%	46701.720	17000.6682 36.40%
C_{max} (ng/mL)	10952.147	2947.7423 26.91%	11424.465	2793.7993 24.45%
T_{max}* (hr)	1.750	0.50 – 4.50	1.750	0.50 – 4.50
T1/2 (hr)	2.206	0.5974 27.08%	2.138	0.5416 25.34%
λ_z (l/hr)	0.334	0.0784	0.348	0.1014

Pharmacokinetic parameter	Test product (T)		Reference product (R)	
	Arithmetic mean	SD CV%	Arithmetic mean	SD CV%
		23.51%		29.17%
AUC_%Extrap_obs	0.918	0.5352 58.30%	0.805	0.4434 55.05%
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 2. Statistical analysis for pirfenidone (fed n=50) (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-t)}$	101.52	95.09% - 108.38%	19.43
C_{max}	93.59	88.92% - 98.51%	15.15
*estimated from the Residual Mean Squares			

The 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters AUC_{0-t} and C_{max} were within the 80-125% acceptance range for pirfenidone after a single dose administration under fed conditions.

- **Safety data**

Pirfenidone tablets 801 mg were well tolerated by the subjects. In total six (06) adverse events were reported during the study. Two subjects reported two adverse events (vomiting) after administration of the test product (T). Three subjects reported four adverse events (3 vomiting and 1 asymptomatic increase in total WBC count) after administration of the reference product (R). No death or serious adverse event occurred during the conduct of the study.

Overall, pirfenidone tablets 801 mg and Esbriet 801 mg film-coated tablets were well tolerated by subjects under fed conditions.

- **Pharmacokinetic conclusion**

Based on the presented bioequivalence study, Pirfenidone AET 801mg film-coated tablets is considered bioequivalent with Esbriet 801mg film coated tablets.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.2.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical aspects

To support the application, the applicant provided one bioequivalence study and literature data on clinical pharmacology, efficacy and safety, which is considered appropriate for a generic marketing authorisation application.

The bioequivalence study design and sampling periods were acceptable, with an adequate wash-out period at greater than five times the $t_{1/2}$. The sampling frequency enabled an adequate estimation of C_{max}.

The study was conducted with the highest strength (801mg) which was safe for use in healthy subjects and under fed conditions. This was in accordance with the methods of administration of the reference SmPC. The population studied was appropriate and the main inclusion and exclusion criteria were in line with the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01). The sample size was in line with the calculation provided in the protocol.

The analytical methods used were acceptable and appropriate. The pharmacokinetic variables and statistical methods applied were appropriate for a single-dose study.

The 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters AUC_{0-t} and C_{max} were within 80-125% acceptance range for pirfenidone after single dose administration under fed conditions. This is in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **).

The two treatments were well tolerated by the subjects (in both periods) enrolled in the study. The safety sections of the product information are in line with the ones of the reference medicinal product Esbriet. In addition, the list of safety concerns, pharmacovigilance plan and risk minimisation measures are identical for both products (see section 2.5.).

Additionally, the applicant requested a biowaiver for Pirfenidone AET 267mg and 534mg film-coated tablets. Initially the applicant stated that the criteria for biowaiver were all fulfilled however there was no mention on the dose linearity of pirfenidone across the strengths applied for. Evidence of dose linearity of pirfenidone across the strengths was provided and the biowaiver accepted.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study Pirfenidone AET 801mg film-coated tablets is considered bioequivalent with Esbriet 801mg film coated tablets.

The results of study 18-VIN-0385 with 801mg formulation CAN be extrapolated to other strengths 267mg and 534mg, according to conditions in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6).

No safety issues have been identified during the bioequivalence study.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	• Photosensitivity and rash • Drug-induced liver injury (DILI) • Gastrointestinal symptoms
Important potential risks	• Severe skin reactions
Missing information	• QT prolongation • Underlying specific cardiac events

2.5.2. Pharmacovigilance plan

There are no additional pharmacovigilance activities. Only routine pharmacovigilance activities will be performed. This includes a specific adverse reaction follow-up questionnaire for drug-induced liver injury (DILI) with pirfenidone.

2.5.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Photosensitivity and rash	Routine risk minimisation measures: *SmPC section 4.2, 4.4 and 4.8* *PIL Section: 2. and 4.* Pirfenidone is available by restricted prescription only. Additional risk minimisation measures: *Prescribers safety checklist*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Drug-induced liver injury	Routine risk communication: *SmPC section 4.2, 4.3, 4.4, and 4.8* *PIL Section: 2.* Pirfenidone is available by restricted prescription only. Additional risk minimisation measures: *Prescribers safety checklist*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up Questionnaire for DILI (Drug induced liver injury) Additional pharmacovigilance activities: *None*
Gastrointestinal symptoms	Routine risk communication: *SmPC section 4.2 and 4.8* *PIL Section: 4.* Pirfenidone is available by restricted prescription only Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	
Severe skin reactions	Routine risk communication: *SmPC section 4.4 and 4.8* *PIL Section: 2. and 4.* Pirfenidone is available by restricted prescription only Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
QT Prolongation	Routine risk communication: *SmPC section: NA* *PIL Section: NA* Pirfenidone is available by restricted prescription only Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Underlying specific cardiac events	Routine risk communication: *SmPC section: NA* *PIL Section: NA* Pirfenidone is available by restricted prescription only Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of pirfenidone film-coated tablet. The reference product Esbriet is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study in healthy, adult under fed conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Pirfenidone AET met the protocol-defined criteria for bioequivalence when compared with the Esbriet. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Pirfenidone AET is favourable in the following indication:

Pirfenidone AET is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH must ensure that at launch all physicians who are expected to prescribe pirfenidone are provided with a physician information pack containing the following:

- Product information (SPC)
- Physician information (safety checklists)
- Patient information (PIL)

The safety checklist about pirfenidone should contain the following key elements related to liver function, drug-induced liver injury and photosensitivity:

Liver function, drug-induced liver injury

- Pirfenidone is contraindicated in patients with severe hepatic impairment or end stage liver disease.
- Elevations of serum transaminases can occur during treatment with pirfenidone.
- There is a need to monitor liver function tests prior to initiation of treatment with pirfenidone and at regular intervals thereafter.
- Close monitoring is required of any patients who develop liver enzyme elevation with appropriate dose adjustment or discontinuation.
- Prompt clinical evaluation and liver function tests for patients who develop signs or symptoms of liver injury.

Photosensitivity

- Patients should be informed that pirfenidone is known to be associated with photosensitivity reactions and that preventative measures have to be taken.

- Patients are advised to avoid or reduce exposure to direct sunlight (including sunlamps).
- Patients should be instructed to use a sunblock daily, to wear clothing that protects against sun exposure, and to avoid other medications known to cause photosensitivity.

The physician information should encourage the prescribers to report serious adverse reactions and clinically significant ADRs of special interest including:

- Photosensitivity reactions and skin rashes
- Abnormal liver function tests
- Drug-induced liver injury
- Any other clinically significant ADRs based on the judgment of the prescriber