10 November 2022
EMA/907420/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pirfenidone Viatris

International non-proprietary name: pirfenidone

Procedure No. EMEA/H/C/005862/0000

Note

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

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List of abbreviations

AE	Adverse event
Afssaps	French Health Products Safety Agency
AGES	Austrian Agency for Health and Food Safety GmbH
ALT	Alanine aminotransferases
ANOVA	Analysis of variance
AST	Aspartate aminotransferases
AUC	Area under the curve
AUC0-24h	Area under the plasma concentration-time curve from time zero to 24 hours
AUC0-∞	Area under the plasma concentration-time curve from time zero to infinity
BCS	Biopharmaceutics classification system
BMI	Body mass index
CDSCO	The Central Drugs Standard Control Organisation
CEP	Certificate of suitability of the European Pharmacopoeia
CFU	Colony forming units
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
Cmax	Maximum plasma concentration
CP	Centralised (application) procedure
CPMP	Committee for Proprietary Medicinal Products
CrCl	Creatinine clearance
CRS	Chemical reference substance (official standard)
CRT	Controlled room temperature
CTM	Clinical trial management
CQAs	Critical quality attributes
CYP	Cytochrome P450
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicine Agency
EWP	The Efficacy Working Party
GCP	Good clinical practice
HDPE	High density polyethylene
HQC	High quality control

ICH	International Council for Harmonisation
ICMR	The Indian Council of Medical Research
IEC	Independent ethics committees
INN	International non-proprietary name
IL	Interleukin
IPC	In-process control
IPF	Idiopathic pulmonary fibrosis
IR	Infrared
IS	Internal standards
HPLC	High performance liquid chromatography
KF	Karl Fischer titration
K3EDTA	Tripotassium ethylenediaminetetraacetic acid
LC-ESI-MS/MS	Liquid chromatography–electrospray ionisation tandem mass spectrometry
LDPE	Low density polyethylene
LLOQ	The lower limit of quantification
LOD	Limit of detection or loss on drying
LoQ	List of questions
LQC	Laboratory quality control
LT	Less than
MA	Marketing authorisation
MAH	Marketing authorisation holder
MEB	Medicines Evaluation Board
MF	Matrix factor
MHRA	Medicines and Healthcare products Regulatory Agency
MQC	Middle quality control
MS	Mass spectrometry
ND	Not detected
NF	National formulary
NLT	Not less than
NMT	Not more than
OC	Other concerns
OECD	The Organisation for Economic Co-operation and Development
OOS	Out of specifications

PCTFE	Polychlorotrifluoroethylene
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
pH	Potential of hydrogen
PIL	Patient information leaflet
PK	Pharmacokinetics
PVC	Poly vinyl chloride
QbD	Quality by design
QC	Quality control
QPD	Qualified person declaration
QTPP	Quality target product profile
QWP	Quality Working Party
R	Reference product
RH	Relative humidity
RLD	Reference listed drug
RRT	Relative retention time
RSD	Relative standard deviation
RT	Retention time
SAS	Statistical software suite
SD	Standard deviation
SmPC	Summary of product characteristics
SOP	Standard operating procedure
T	Test product
t1/2	The terminal elimination half-life
TAMC	Total aerobic microbial count
TGF-	Transforming growth factor-beta
Tmax	Time to maximum plasma concentration
TNF-α	Tumour necrosis factor-alpha
TYMC	Total yeast and mould count
USAN	United States adopted name
λZ	Elimination rate constant

* This is a general list of abbreviations. Not all abbreviations will be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Viatris Limited submitted on 10 September 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Pirfenidone Viatris, 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 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 Viatris 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 data 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(s): EU/1/11/667
- Bioavailability study number(s): 19-VIN-0275

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: Tomas Radimersky

The Rapporteur appointed by the PRAC: Rhea Fitzgerald

The application was received by the EMA on	10 September 2021
The procedure started on	25 November 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 February 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	01 March 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 March 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 July 2022

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	22 August 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 September 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	15 September 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	10 October 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	02 November 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 Viatris on	10 November 2022

2. Scientific discussion

2.1. Introduction

Idiopathic pulmonary fibrosis (IPF), a highly heterogeneous chronic, fibrosing type of interstitial pneumonia, is characterised by a progressive loss of lung function, potentially leading to acute respiratory decline and death. It is limited to the lungs, occurs primarily in older adults and is associated with histological and/or radiological characteristics of usual interstitial pneumonia. Studies in Europe suggest an annual incidence of 0.22–7.4 cases per 100,000 and a prevalence of 1.25–23.4 cases per 100,000 in the population. The prognosis is poor, with a median survival time estimated at 2–5 years from the time of diagnosis. The 5-year survival rate is approximately 20 % and the mortality burden associated with IPF is higher than that of some cancers. Targeting mechanisms and mediators involved in tissue fibrosis has become an important strategy of IPF treatment.

This is a generic application of medicinal product Pirfenidone 801 mg tablets according to Article 10(1) of Directive 2001/83/EC, as amended submitted through a centralised procedure. The essential similarity is claimed to Esbriet 801 mg film-coated tablets containing the same active substances in the same strengths approved via centralised procedure (EU/1/11/667).

Pirfenidone, a synthetic pyridine compound, inhibits the progression of fibrosis and loss of lung function in patients with IPF via its antifibrotic, anti-inflammatory and antioxidant properties. In animal models of pulmonary fibrosis, pirfenidone reduced production of profibrotic and proinflammatory cytokines, such as transforming growth factor-β1 and lung basic fibroblast growth factor and suppressed both decreases in interferon-γ and elevations in interleukin (IL)-1β, IL-6, IL-12p40, tumor necrosis factor-α and monocyte chemoattractant protein-1. The antifibrotic properties of pirfenidone appear to involve inhibition of collagen fibril formation, as shown by an *in vitro* study in primary human fibroblasts from patients with IPF and healthy donors.

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: cellulose, microcrystalline (E 460), croscarmellose sodium (E 468), povidone (E 1201), silica, colloidal anhydrous (E 551) and magnesium stearate (E 572).

Film-coating: poly(vinyl alcohol) (E 1203), titanium dioxide (E 171), macrogol (E 1521), talc (E 553b), iron oxide yellow (E 172) (in 267 mg and 534 mg film-coated tablet only), iron oxide red (E 172) (in 534 mg and 801 mg film-coated tablet only) and ferric oxide black (E 172) (in 801 mg film-coated tablet only).

The product is available in transparent PVC/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 following structure:

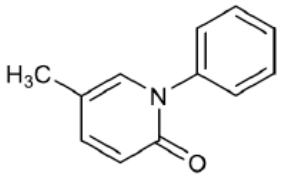

Figure 1: active substance structure

Pirfenidone is a white or pale yellow, not hygroscopic, crystalline powder which is sparingly soluble in water but freely soluble in ethanol and slightly soluble in heptane.

The active substance has a non-chiral molecular structure.

Pirfenidone primarily exists in a single stable crystalline form designated as Form A.

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 active substance is manufactured by one manufacturer (Tyche Industries Limited, India).

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The CEP specifies that the active substance is packaged in double polyethylene bags (outer black) placed in a polyethylene drum as approved by the EDQM.

2.2.2.3. Specification

The CEP confirms that the pirfenidone is suitably controlled according to the Ph. Eur. monograph (no. 2856).

The active substance specification shown in Table 1 is based on the Ph. Eur. monograph and includes tests for: appearance, identification (IR), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), related substances (Ph. Eur.), assay (Ph. Eur.), particle size (laser diffraction) and microbial enumeration/specified microorganism (in-house methods, tested on the first three batches only).

The active substance specification proposed by the finished product manufacturer is the same as the one from the active substance manufacturer with an additional test for particle size and microbiological purity. Microbiological purity will be tested on the first three batches. The additional test for particle size has been adequately described and validated in accordance with ICH Q2. The specification limit is justified. The test for microbiological purity has been verified.

Particle size distribution is not a critical parameter with respect to the pharmaceutical performance of the finished product. Pirfenidone is a BCS class I substance and the dissolution of the active substance is not influenced by the particle size distribution.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for eight commercial scale batches of the active substance 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

The CEP includes a re-test period of 36 months if stored in the specified container closure system (double polyethylene bags (outer black), placed in polyethylene drums).

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is presented as film-coated tablets containing pirfenidone as active substance. Three strengths are proposed to be authorised:

- 267 mg: yellow, oval shaped, approximately 13.15 x 6.15 mm biconvex film-coated tablets, plain on both sides.
- 534 mg: orange, oval shaped, approximately 16.25 x 8.45 mm biconvex film-coated tablets, plain on both sides.
- 801 mg: brown, oval shaped, approximately 20.15 x 9.45 mm biconvex film-coated tablets, plain on both sides.

The three strengths can be sufficiently differentiated by colour and size.

Pirfenidone Viatris is a generic of the product Esbriet and the aim of the formulation development was to develop film-coated tablets which are essentially similar to the reference product. The pharmaceutical development of the finished product contains QbD elements. The formulation and manufacturing development have been evaluated through the use of risk assessments. Definition of the quality target product profile (QTPP, table below) allowed identification of potential critical quality attributes (CQAs: identity, assay, blend/content uniformity, dissolution, related substances, residual solvents and microbial limits), which were then investigated during development studies.

Table 1: Quality target product profile for Pirfenidone Viatris

Quality Target Product Profile (QTPP) Attributes		Target	Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement
Dosage design		Immediate release tablets without scoreline and with film coating	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same administration route.
Dosage strength		267 mg, 534 mg, 801 mg	Pharmaceutical equivalence requirement: same strength.
Pharmacokinetics		Immediate release enabling T_{max} to be bioequivalent to RLD	Bioequivalence requirement. Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical attributes	Pharmaceutical equivalence requirement: Meeting the compendial or other quality standards.	
	Identification		
	Assay		
	Related substances		
	Content uniformity		
	Dissolution		
	Residual solvents		
	Water content		
	Microbial limits		
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping.
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that administration of formulation with food reduced pirfenidone Cmax.
Alternative methods of administration		None	None are listed in the RLD label.

The polymorphic form of the active substance was studied and was found to be stable for up to 6 months under accelerated conditions (40°C / 75% RH). As indicated in the active substance section,

the particle size of the active substance is controlled in the active substance specification but is not a critical parameter as regards dissolution due to the high solubility of the active substance (BCS class I substance).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. with the exception of the colourants iron oxide yellow, red and black which are also compendial and comply with the United States Pharmacopoeia/National Formulary. 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 2.2.1 of this report.

The excipients are similar to the excipients used in the reference product. Results from compatibility studies of the excipients with the active substance have been presented and compatibility has been sufficiently demonstrated.

The excipients in the tablet core are dose proportional. The tablet core weight as well as the total weight of the coating layer are also dose proportional. This supports to use of a biowaiver of strengths as further discussed below.

The development of the dissolution method was described, and the discriminatory power of the dissolution method has been demonstrated. The discriminatory power was demonstrated by testing a batch that contained increased concentration of binder povidone. For Quality Control testing, a method utilizing a USP Apparatus II with 900 mL of 0.1 N HCL with a paddle speed of 50 rpm was selected.

An *in vivo* bioequivalence study was conducted with relevant batches of the test and the reference medicinal products in the highest strength (801 mg) and the two products were found to be bioequivalent. Please refer to the clinical section for further details of this study. The test product used in the bioequivalence study is identical to the proposed commercial formulation.

Comparative dissolution profiles of the batches of the test and reference product used in the bioequivalence study (highest strength – 801 mg) were presented for three media (0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8). Dissolution of the active substance from both test and reference product was >85% at 15 minutes in all tested media. The results demonstrate that the dissolution profiles are similar.

To justify a biowaiver for the two lower-strength presentations of Pirfenidone Viatris (267 mg and 534 mg), a comparative dissolution study was conducted in three media (0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8). Results demonstrate that the corresponding dissolution profiles are similar to the highest-strength tablet.

The product meets the general requirements outlined in the Guideline on Investigation on Bioequivalence (CHMP/EWP/QWP/1401/98 Rev 01) to justify a biowaiver of strength for the two lower strengths (267 mg and 534 mg), namely a) the pharmaceutical products are manufactured by the same manufacturing process, b) the qualitative composition of the different strengths is the same, c) the composition of the strengths are quantitatively proportional, and d) appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing. Based on the information provided the biowaiver can be accepted.

Formulation development studies have been described (e. g., including glidant in the extra granular portion, increasing the concentration of disintegrant in the extra granular portion, decreasing of binder concentration, optimisation of the concentration of other excipients, including film coat weight) and the flow of the blends and other physical parameters were examined together with comparative dissolution profiles of test and reference product to support the final composition of the finished product.

The development of the manufacturing process for the finished product has been described. As pirfenidone displays very poor flowability, a wet granulation process was selected to avoid material

flow processing problems. A risk assessment of the overall finished product manufacturing process was performed to identify the high-risk steps that may affect the CQAs of the finished product. Subsequently, the intermediate CQAs of the output material from each process step that impact the finished product CQAs were identified. For each process step, a risk assessment was conducted to identify potentially high-risk process variables which could impact the identified intermediate CQAs and the finished product CQAs. These variables were then investigated in order to better understand the manufacturing process and to develop a control strategy to reduce the risk. The manufacturing process used to manufacture the batch used for the bioequivalence study is the same as proposed for commercial manufacturing.

The primary packaging is transparent PVC/PCTFE – aluminium blisters. The material complies with Ph. Eur. and EC requirements. 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 finished product is manufactured at one manufacturing site (Chemo India Formulations Pvt. Ltd., India), with further sites involved for secondary packaging and QC testing.

The manufacturing process consists of 12 main steps: manufacture of the binder solution, dry mixing, wet granulation, sieving, fluidised bed drying, sieving, pre-lubrication, lubrication and final blend, holding time (if necessary), compression, holding time (if necessary) and coating.

The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. An acceptable process validation scheme has been submitted.

Coating material is added in excess up to about 30% of the defined quantity to compensate possible loss during the film-coating process. This is acceptable.

The maximum batch manufacturing time from start of product manufacture to completion of packaging into the final primary container for marketing has been defined (6 months).

A bulk holding time study was conducted. Stability data justify a maximum hold time of two months for the blend (before tabletting) and cores (before coating) without special storage conditions.

The start of shelf-life of the finished product is determined in accordance with Note for Guidance on Start of Shelf-life of the Finished Dosage Forms (CPMP/QWP/072/96).

2.2.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC, UV), water content (KF), uniformity of dosage units (Ph. Eur.), assay (HPLC), dissolution (Ph. Eur.), related substances (HPLC), identification of titanium dioxide (colour reaction) and microbial enumeration/specified microorganism (Ph. Eur.).

The finished product specification includes all relevant test parameters for this type of dosage form and complies in general with Ph. Eur. and the EU/ICH guidelines. All proposed acceptance criteria have been sufficiently justified. The absence of routine microbial testing is acceptable in line with ICH Q6A., decision tree #8. The finished product specification is acceptable.

In response to a major objection raised by CHMP during the procedure, the limit for dissolution testing has been tightened based on available data from the batch used for the bioequivalence study. The major objection is resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

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 (Option 2b). Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes 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 there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Batch analysis results are provided for 3 batches of each strength (267 mg, 534 mg and 801 mg) manufactured at commercial scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.2.3.4. Stability of the product

Stability data has been presented from two batches of each strength. Due to the similarity of the different strength tablets, it is acceptable in this case to test 2 batches per strength. The batches were manufactured at the minimum commercial batch size at the manufacturing site proposed for commercial manufacturing (the maximum batch size is ten times higher). The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. Batches were stored for 12 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines. Samples were tested for appearance, water content, assay, dissolution, related substances and microbiological purity. The analytical procedures used were the same as for release and are stability indicating. No significant changes were observed.

One batch of the lowest strength (267 mg) and one batch of the highest strength (801 mg) were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results demonstrate that the finished product is not sensitive to light.

Furthermore, results from forced degradation studies have been presented. The finished product was exposed to acid and basic hydrolysis, peroxide oxidation, dry heat as well as humid heat and was found to be stable under all conditions.

In addition, a stability study to support the holding time of the bulk tablets was conducted. Each strength of the finished product was tested. Stability data was provided from batches stored for 6 months under long term conditions (25ºC / 60% RH). Samples were tested for appearance, water content, assay, dissolution, related substances and microbiological purity. All results were within specification. A hold time of 6 months for the bulk tablets is considered acceptable for all strengths of the finished product when stored in the proposed packaging. Tablets in bulk are packed in double LDPE plastic bags with a bag of desiccant between both bags. The bags are then placed in a HDPE container.

Based on available stability data, the proposed shelf-life of 2 years without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

2.2.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Pirfenidone Viatris is a generic of the reference product Esbriet. Information on the manufacture and stability of the active substance has not been presented in the dossier as this information has been assessed by the EDQM before issuing the Certificate of Suitability. A major objection raised during the procedure in relation to the specification limit for dissolution testing of the finished product has been satisfactorily 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. 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

Not applicable.

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

The applicant performed Phase I exposure assessment, Phase II fate and effects analysis, PBT assessment and calculated the potential risks for the aquatic environment following the PECsw of 0.36 µg/L and the PNEC of 1.06 mg/L (determined from a NOEC value of 10.6 mg/L from a fish chronic toxicity study by using an assessment factor of 10). Pirfenidone has been found not to be readily biodegradable, with a DT50 value of >120 days for the total water/sediment system, thus being considered as potentially persistent. The log Kow of pirfenidone was reported to be far below 4.5 (i.e., 0.9), which implies limited potential for bioaccumulation. The overall environment risk of pirfenidone was evaluated as "insignificant" based on the PEC/PNEC ratio of < 0.001.

Risks for STP and groundwater have not been determined by the applicant. However, given the NOEC values of 100 mg/L for microorganisms and of 94 mg/L for D. magna and the PECsw value of 0.36 µg/L, assuming PECgw of 0.36x0.25 = 0.09 µg/L, no apparent risks are envisaged for these compartments.

The provided information is considered sufficient to derive a conclusion on the environmental risk of pirfenidone. According to the outputs of the ERA, no apparent risk is foreseen in relation to the use of the generic product containing pirfenidone as active substance. No further data are deemed necessary to support this conclusion.

Table 2: Summary of main study results

Substance (INN/Invented Name): Pirfenidone					
CAS-number (if available): 0053179-13-8					
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	0.9			not B
Persistence	DT50 or ready biodegradability	> 120 days			P
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.36	µg/L			> 0.01 threshold (Y)
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	18.3	mg/L	Green algae (*Raphidocelis subcapitata*)
Daphnia sp. Reproduction Test	OECD 211	NOEC	94	mg/L	

Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	10.6	mg/L	Fathead minnow (Pimephales promelas)

2.3.3. Discussion on non-clinical aspects

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.

According to the outputs of the ERA, no apparent risk is foreseen in relation to the use of the generic product containing pirfenidone as active substance. No further data are deemed necessary to support this conclusion.

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 Viatris 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 (19-VIN-0275). 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) 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 pharmacokinetics and pharmacodynamics as well as 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

Justification of biowaiver:

All conditions described in Guideline on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) from a) to d) are fulfilled, it is sufficient to establish bioequivalence with only one strength.

"If a test product constitutes several strengths, it is sufficient to establish bioequivalence with only one strength, provided that all of the below conditions are fulfilled**"**.

a) The pharmaceutical products are manufactured at the same site by the same manufacturer and manufacturing process.

b) Linear pharmacokinetics, i.e., proportional increase in AUC and C_{max} with increased dose, over the therapeutic dose range.

c) The qualitative composition of the different strengths is the same.

d) The composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products, coating components, colour agents and flavours are not required to follow this rule).

e) Appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing"

Bioequivalence studies for Pirfenidone 267 mg and 534 mg film-coated tablets can be waived.

Once *in vivo* as well as *in vitro* equivalence between the innovator product (Esbriet 801 mg film-coated tables) and the bio batch (Pirfenidone 801 mg film-coated tablets) was demonstrated, a comparative dissolution study was performed. The biowaiver for the lower dosage of Pirfenidone 534 mg and 267 mg film-coated tablets has been justified.

Tabular overview of clinical studies

To support the application, the applicant has submitted one bioequivalence study.

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
19-VIN-0275	To compare and evaluate a single-dose oral bioavailability of Pirfenidone 801 mg film-coated tablets of Chemo India Formulation Pvt. Ltd. and Esbriet 801 mg film-coated tables of Roche Registration GmBH in Healthy, Adult, Human Subjects under Fed Conditions as well as to monitor the safety and tolerability of subjects.	An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover pivotal oral bioequivalence study of Pirfenidone 801 mg film-coated tablets and Esbriet 801 mg film-coated tables, in Healthy, Adult, Subjects under fed conditions.	**Test product (T):** Pirfenidone, 801 mg, oral administration **Reference product (R):** Esbriet, 801 mg, oral administration	60 Subjects enrolled;54 Subjects completed the study	Healthy, adult, human subjects	Single-Dose	Completed

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 19-VIN-0275

An open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, two-way crossover pivotal oral bioequivalence study of Pirfenidone 801 mg film-coated tablets and Esbriet 801 mg film-coated tablets, in Healthy, Adult, Subjects under fed conditions.

Methods

- **Study design**

This study was designed as an open label, balanced, randomised, two-treatment, two-sequence, two-period, single-dose, two-way crossover oral bioequivalence study in healthy, adult, human subjects under fed conditions.

The objective of the study is to compare and evaluate a single-dose oral bioavailability of Pirfenidone 801 mg film-coated tablets and Esbriet 801 mg film-coated tables in healthy, adult, subjects under fed conditions as well as to monitor the safety and tolerability of subjects.

In the present study, the two formulations were administered as a single 801 mg oral dose to 60 healthy adult, human (48 Males and 12 Females) subjects under fed conditions as per the following randomised, 2-treatment, 2-sequence, 2-period, crossover design:

Table 3: Study design

	Period 1	Period 2
Sequence 1 (n=30)	Test (T)	Reference (R)
Sequence 2 (n=30)	Reference (R)	Test (T)

Subjects were housed in the clinical facility from -36.00 hours prior to schedule time of dosing and left the facility after 24.00 hours post-dose blood sample collection in each study period.

Subjects were instructed during screening to refrain from smoking, chewing tobacco, pan or pan masala, gutkha, masala (containing betel nut and tobacco) and from consuming any alcoholic products, xanthine-containing foods or beverages (like chocolate, tea, coffee or cola drinks) for 48.00 hours prior to admission of Period 01 till last blood sample was collected in the study.

Subjects were instructed during screening to refrain from consuming grapefruit or grapefruit juice containing products for 72 hours prior to admission of Period 01 till last blood sample was collected in the study. Subjects were not allowed to have the same from admission till discharge in each period.

Subjects were instructed to avoid or minimise exposure to sunlight (including through windows, from sunlamps and tanning beds), to avoid other medicinal products known to cause photosensitivity, to use a sunblock (SPF50 or higher) and to wear clothing that protects against sun exposure during the study.

Pirfenidone causes dizziness and fatigue and had moderate influence on the ability to drive or use machines, therefore subjects should take care while driving or operating machinery if they experience these symptoms.

Subjects received dinner on check-in day and standard meal at -24.00, -20.00, -16.00, -12.00 hours prior to dosing of investigational product and at about 05.00, 08.00 and 12.00 hours after dosing of investigational product in each study period. During housing, all meal plans were kept identical for all the periods. In case, meal, vital sign measurements and blood sample collection times were coincided, then samples followed by vital sign measurement was given priority over meal.

Drinking water was not allowed from one hour before dosing till four hour after dosing (except 240 ± 2 mL of water given for dosing and 240mL of water given at 02 hours post-dose). At 2 hrs post dose all the subjects consumed the water within 5 minutes. Before and after that, drinking water was allowed at all times.

Subjects were asked to remain in sitting posture and was not allowed to lie down or sleep for at least 4 hours after dosing (except for any procedural requirements and using bathroom) unless clinically indicated. Subjects were allowed to rise for brief periods under supervision (i.e. in order to use the washroom facilities or for any procedural requirements like blood sample collection and vital signs measurements) during the restriction period. Thereafter, subjects were allowed to engage in normal activities while avoiding severe physical exertion.

Subjects were instructed not to consume any prescribed medication and OTC medical products including herbal remedies and vitamin supplements within 30 days prior to admission in Period 01 till the completion of the study.

Following high-calorie, high-fat breakfast was served before dosing:

Table 4: Meal composition

BREAKFAST BEFORE DOSING (cooked weight)

Cheese Sandwich -80gm
Whole Milk - 240mL
Egg Omelet (Plain) - 80gm
Chicken Fry - 40gm
Potato Fry - 22gm
Tomato Chutney - 20mL

Food items (Raw weight)		Amount gm	CHO gm	Protein gm	Fat gm	Calories kcal
Cheese Sandwich -	Bread	50	29.00	3.20	0.60	134.30
	Cheese	30	1.96	7.20	7.36	102.8
Whole Milk -	Milk	240ml	12.00	7.92	14.40	209.28
	Sugar	5	5.00	0.00	0.00	20.00
Egg Omelet (Plain) -	Eggs	80(2no.)	0.00	10.64	10.64	138.30
	Butter	5	0.00	0.00	4.05	36.45
Chicken Fry -	Chicken	40	0.00	10.36	0.24	43.60
	Oil	10ml	0.00	0.00	10.00	90.00
Potato Fry -	Potato	75	16.95	1.20	0.08	73.28
	Oil	15ml	0.00	0.00	15.00	135.00
Tomato chutney		20ml	0.50	0.10	0.19	4.11
Total (gm-approx)			**65.41**	**40.62**	**62.56**	
Total (Calories)			**261.64**	**162.48**	**563.00**	987.12
%			**26.51**	**16.46**	**57.03**	100.00

(1gram carbohydrate and protein is equal to 4 kcal and 1gram of fat is equal to 9 kcal)

Sampling schedule was planned to provide an adequate estimation of C_{max} and to cover the plasma concentration-time curve long enough to provide a reliable estimate of the extent of absorption.

A total of twenty-six (26) blood samples were collected during each study period. The pre-dose (00.00 hour) blood sample of 3.0 mL was collected within one hour before dosing.

Post-dose blood samples of 3.0 mL each was drawn at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours after dosing in each study period.

Two blood sampling deviations were identified in phase II.

Table 5: Protocol deviations

Project No: 19-VIN-0275 Form Title: Protocol deviation

Sr. No.	Period	Date	Subject No.	Time Point (hr)	Scheduled Time	Actual Time	Actual Deviation (Min)	*Reason for deviation	Deviation as per protocol(Min)
1.	02	[redacted]	[redacted]	00.25	09:45	09:48	03	CB	01
2.	02	[redacted]	[redacted]	00.25	09:35	09:40	05	CB,DW	03

Subjects were instructed not to consume any prescribed medication and OTC medical products including herbal remedies and vitamin supplements within 30 days prior to admission in Period 01 till the completion of the study. Following subjects were given concomitant medication as a treatment of adverse event during the course of study.

Table 6: Concomitant medication

Subject Number	Brand Name	Generic Name	Start Date and Time	Dose	Frequency	Route of administration	Duration of Treatment	Drug-Drug Interaction
[redacted]	Tablet Zerodol SP	Aceclofenac, Serratiopeptidase and Paracetamol	[redacted]	100mg, 15mg and 325mg	Twice a day	Oral	Two days	No
	Betadine Ointment	Povidone iodine		10 %w/w	Twice a day	Local	Two days	No
[redacted]	Tablet Crocin advance	Paracetamol	[redacted]	500 mg	Once only	Oral	NA	No

- **Test and reference products**

Pirfenidone Viatris 801 mg film-coated tablets manufactured by Chemo India Formulations Pvt. Ltd. Hyderabad has been compared to Esbriet 801 mg film-coated tables manufactured by Roche Registration GmBH.

- **Population(s) studied**

Based on the available literature, the maximum intra-subject variability observed was found to be ~21%; the sample size computation was determined using SAS® by considering the following assumptions:

a. T/R ratio = 0.90-1.11

b. Intra-Subject CV (%) ~ 21%

c. Significance Level = 5%

d. Power = 90%

e. Bioequivalence Limits = 80.00-125.00%

Based on the above estimate, a sample size of 55 subjects would be sufficient to establish bioequivalence between formulations with adequate power. However, considering the dropouts and/or withdrawal subjects, a sample size of 60 subjects (48 Males and 12 Females) were randomised and enrolled in the study.

A total of 60 (48 Male and 12 Female) healthy, adult, human subjects were enrolled in the study. Weight, height, BMI and age of each subject were recorded during screening. Subjects aged between 21 and 44 years (including both), Body Mass Index (18.81 to 29.83 kg/m2, (both inclusive)) with minimum of 50.30 kg weight were included in the study. A general medical history, laboratory investigations, clinical examination (including vital sign (blood pressure, oral temperature, radial pulse rate and respiratory rate) and physical examination and systemic examination), ECG recordings and urine pregnancy test (only for female subjects) were conducted at the time of screening for all subjects. All subjects in the study were Asian.

Following subjects were discontinued from the study:

- 3 subjects were withdrawn from the study due to adverse event after dosing of period 01 (Vomiting).
- 1 subject was withdrawn from the study due to adverse event before dosing of period 02 (Vomiting).
- 2 subjects were withdrawn from the study due to adverse event after dosing of period 02 (Vomiting).
- 1 subject was withdrawn from the study (did not complete high fat high calorie breakfast of period 01) and was replaced with extra subject.
- 1 subject withdrew his consent from the study before dosing of period 01.

Table 6: **List of demographic profiles of enrolled subjects (n=60)**

Demographic	Age (Years)	Height (cm)	Weight (Kg)	BMI (Kg/m²)
Mean	32.15	163.22	62.97	23.68
Standard Deviation	6.31	7.23	9.20	3.37
Median	31.00	165.00	61.40	23.31
Standard Error Mean	0.81	0.93	1.19	0.44
Maximum	44.00	176.00	85.90	29.83
Minimum	21.00	145.00	50.30	18.81

Table 7: **List of demographic profiles of completed subjects (n=54)**

Demographic	Age (Years)	Height (cm)	Weight (Kg)	BMI (Kg/m²)
Mean	31.82	163.61	63.09	23.60
Standard Deviation	6.33	6.83	9.48	3.40
Median	31.00	165.00	61.30	23.41
Standard Error Mean	0.86	0.93	1.29	0.46
Maximum	44.00	176.00	85.90	29.83
Minimum	21.00	145.00	50.30	18.81

Randomisation

Randomisation was carried out using SAS® (SAS Institute Inc., USA) version 9.4. Randomisation was done in blocks using PROC PLAN such that the design was balanced.

The order of receiving the Test (T) and Reference (R) product for each subject during each period of the study was determined according to the randomisation schedule. In the present study, the two formulations were administered as a single 801 mg oral dose to 60 healthy adult, human (48 Males and 12 Females) subjects under fed conditions as per the following randomised, 2-treatment, 2-sequence, 2-period, crossover design:

Table 8: **Study design**

	Period 1	Period 2
Sequence 1 (n=30)	Test (T)	Reference (R)
Sequence 2 (n=30)	Reference (R)	Test (T)

Blinding

This study designed as a randomised open-label study. However, all analytical staff was blinded to the sequence of administration of Test (T) and Reference (R) formulations to individual subjects until after completion of study sample analysis.

- **Analytical methods**

The plasma concentrations of pirfenidone in the study samples were determined by a validated LC-ESI-MS/MS method. The analyte and internal standard (pirfenidone-d3) were extracted from 0.100 mL of K3EDTA human plasma using solid-phase extraction technique. The calibration curve standard range was from 50.00 ng/mL to 30000.00 ng/mL. Quantitation was based on peak area ratio of analyte versus internal standard. A least squares linear regression with weighing factor 1/x2 was used.

The samples were stored at -78 ± 8°C. The analysis was completed within nineteen (19) days from the date of the first sample collection to the last day of analysis. Long-term stability of pirfenidone in human plasma was confirmed for 35 days at -20±5°C and at -78±8°C.

In the study, sixty (60) subjects were dosed in the Period I. A total of fifty-four (54) subjects completed the trial and were included in the final statistical analysis. In each period, a total of twenty-six (26) blood samples were collected from each subject. Theoretical number of samples expected as per protocol was 6240 (60 subjects x 2 periods x 26 blood collections per period x 2 aliquots). Samples of all 60 subjects were analysed. There were 396 samples not received (both aliquots from withdrawn subjects). Total number of samples analysed was 2922.

Different stock solutions were used for preparation of calibration standards and QC samples. Calibration curve standards and quality control samples were stored in the freezer maintained at -78 ± 8°C. The quality control samples were prepared at five concentration levels (LLOQ QC, LQC, MQC1, MQC2 and HQC).

The mean coefficient of determination (r2 value) was 0.9988.

Table 9: Summary of accuracy and precision for back-calculated concentrations of pirfenidone in calibration standards and in QC samples

	Calibration standards	QC samples
Accuracy (%bias)	-2.55 to 2.66 %	-3.79 to -1.61 %
Precision	1.73 to 2.90 %	1.49 to 3.76 %

One analytical run was rejected and repeated. Three (03) individual pirfenidone samples (0.1%) were re-assayed as per SOP.

A total of 198 study samples were re-analysed for the incurred sample reproducibility test. A total of 100 % of the re-analysed samples met the criteria of assay reproducibility for pirfenidone.

Bioanalytical method validation

A LC-ESI-MS/MS method for the determination of pirfenidone K3EDTA human plasma was developed and validated. Validation results are presented in the Method Validation Report VIN-BRD-MV-1232 and in Amendment 01 (ruggedness and long-term stability in matrix).

Table 10: summary of the validation results

Linearity (weighted $1/x^2$)	r^2 mean 0.9975
Calibration curve range	50.000 ng/mL to 30000.000 ng/mL
Within-run precision	≤ 2.63 %
Within-run accuracy	-7.66 % to 2.08 %
Between-run precision	≤ 4.21 %
Between-run accuracy	-2.82 % to 1.42 %
LLOQ	Accuracy -2.81%; precision 2.33%
Specificity	09 out of 09 human plasma lots passed (incl. normal, haemolytic and lipidemic lots), no interference peak.
IS-normalised MF	0.42 and 0.27 %CV (LQC and HQC)
Dilution integrity (140000 ng/mL diluted 10-fold)	The % CV and accuracy within the acceptance limit.
Overall recovery of analyte	105.64 % (6.57 %CV)
Overall recovery of IS	107.09 % (0.90 %CV)

In addition, selectivity in presence of concomitant medication, batch size experiment, ruggedness in case of different analyst, equipment or column, carry-over, reinjection reproducibility and stability of pirfenidone in solutions and in matrix were investigated.

Table 11: Summary of stability results of pirfenidone

Whole blood stability	2 hours and 30 min at wet ice bath (below 10°C) and at ambient temperature
Short-term stability in matrix	07 hours at ambient temperature
Post-preparative stability	20 hours at ambient temperature
Autosampler stability	77 hours at 5±3°C
Freeze-thaw stability	5 cycles at -20±5°C and at -78±8°C
Long-term stability in matrix	35 days at -20±5°C and at -78±8°C

- **Pharmacokinetic variables**

The pharmacokinetic parameters were calculated using non-compartmental model by using Phoenix WinNonlin® 8.0 (Pharsight Corporation, USA).

Primary pharmacokinetic parameters were

- AUC_{0-t}: The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, where t = time of last measurable concentration, calculated using linear trapezoidal method.
- C_{max}: Maximum measured plasma concentration over the time span specified.

Secondary pharmacokinetic parameters were

- $AUC_{0-\infty}$: The area under the plasma concentration versus time curve from time 0 to infinity. $AUC_{0-\infty} = AUC_{0-t} + C_{last} / \lambda_Z$; where C_{last} is last measurable concentration, λ_Z is elimination rate constant.
- T_{max}: Time of the maximum measured plasma concentration. If the maximum-value occurs at more than one time point, T_{max} is defined as the first time-point with this value.
- λ_Z: The elimination rate constant associated with the terminal (loglinear) portion of the curve. Estimated by linear regression of time vs. log concentration.
- $t_{1/2}$: The terminal elimination half-life, calculated as (ln2)/ λ_Z.
- AUC_%Extrap_obs: Percentage of $AUC_{0-\infty}$ due to extrapolation from T last to infinity and calculated by: $100*(AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty}$. AUC_%Extrap_obs measures the residual area.

- **Statistical methods**

Results

A total 60 subjects were enrolled in the study. Fifty-four (54) subjects completed both periods of the study. Pharmacokinetic and Statistical analyses were performed over 54 subjects.

Table 12: Pharmacokinetic parameters for pirfenidone (non-transformed values)

Pharmacokinetic parameter	Test (N=54)		Reference (N=54)	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$ (hr*ng/mL)	45001.51	15213.33	40971.46	11086.05
$AUC_{(0-\infty)}$ (hr*ng/mL)	45391.27	15319.56	41356.62	11209.28
C_{max} (ng/mL)	10817.78	3396.87	10053.50	2599.13
T_{max}* (hr)	1.75	0.25 – 6.00	1.88	0.50 – 4.50
AUC_{0-t}	area under the plasma concentration-time curve from time zero to last observed concentration at time			
$AUC_{0-\infty}$	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 13: Statistical analysis for pirfenidone (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	90% Confidence Interval	CV%*
$AUC_{(0-t)}$ (hr*ng/mL)	107.19%	(102.06%, 112.57%)	15.30%
C_{max} (ng/mL)	105.53%	(98.96%, 112.53%)	20.14%
* estimated from the Residual Mean Squares			

For C_{max} of pirfenidone, there was statistically significant period effect (p-value=0.0001) on 5% significance level.

For AUC_{0-t} of pirfenidone, there were statistically significant period effect (p-value=0.0001) and formulation effect (p-value=0.0214) on 5% significance level.

Justification of significant period effect:

Significant period effect could possibly reflect different positioning, timing and degree of physical activity, timing and composition of food/beverages ingested, or the temperature of the water administered in the two periods. To our knowledge, the conditions were maintained similar for both the periods; therefore, it seems none of these are applicable in this study. However, it is possible that the psychological status of the subjects differed between the two periods, which may in turn effect on concentration data. The plasma samples of each subject of both the periods are analysed all together and in a sequence in which the blood samples were collected. So, there are very less chance of having analytical error. Also, in each period both the products were dosed (Test and Reference), so period effect is not expected to influence the comparison of both the products using 90% confidence interval.

Justification of significant formulation effect:

Significant treatment effect or formulation effect can be present when the treatment mean square is small. Significant difference can occur at the moment the variability is low or the number of volunteers sufficiently high. Significant treatment effect or formulation effect can simply be ignored as the decision of equivalence is based on the Schuirmann test and the 90% confidence interval is within the equivalence boundaries.

- **Safety data**

Following subjects reported adverse events during the study. A total of nine (9) adverse events occurred during the study. The adverse events were not life threatening and did not require subjects' hospitalisation.

The adverse event reported during the study was analysed for onset, relationship, severity, seriousness, duration and resolution.

The safety analysis includes all subjects who dosed in the study with either test or reference product. Total nine (9) AEs were reported by eight (8) (08/60, 13.33%) subjects during conduct of the study.

Three (3) (03/09, 33.33%) adverse events were reported by three subjects (3) (03/57, 5.26%) after administration of Test product (T).

Six (6) (06/09, 66.67%) adverse events were reported by five subjects (5) (05/59, 8.47%) after administration of the Reference product (R).

Out of nine (9) AEs, seven (7) (07/09, 77.78%) AEs were possibly related with study drug and two (2) (02/09, 22.22%) AEs were not related with study drug.

No serious adverse event (SAE) or no death was reported for any of the subjects enrolled in this study.

The safety profiles for all treatments indicated that single dose of the study drugs were well tolerated by the all subjects.

Treatment-related severity and relationship of adverse events are mentioned in below table:

Table 14: Treatment-related severity and relationship of adverse events

	Severity			Relationship with study drug			
Treatment	Mild	Moderate	Severe	Unlikely	Possible	Probable/ Likely	Not Related
Test (T)	01	02	00	02	01	00	00
Reference (R)	06	00	00	00	06	00	00
Total	07	02	00	02	07	00	00

There were no deaths and significant adverse events during the conduct of this study.

2.4.2.2. Pharmacodynamics

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

2.4.3. Discussion on clinical aspects

To support the application, the company has submitted one (1) bioequivalence study. The applicant has conducted an open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, two-way crossover pivotal oral bioequivalence study of Pirfenidone 801 mg film-coated tablets and Esbriet 801 mg film-coated tables, in healthy, adult, human subjects under fed Conditions. Biowaiver for Pirfenidone 267 mg and 564 mg was justified and is acceptable.

Pirfenidone 801 mg film-coated tablets when compared with Esbriet 801 mg film-coated tablets meets the bioequivalence criteria in terms of rate and extent of absorption after administration of single dose as set in the protocol. Therefore, bioequivalence has been demonstrated.

Seven (7) adverse events with possible relationship with study drug were identified, 6 for reference product, 1 for test product. No severe adverse events, significant adverse events or deaths were reported.

The safety profiles for all treatments indicated that single dose of the study drug was well tolerated by all subjects.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study Pirfenidone Viatris 801 mg is considered bioequivalent with Esbriet 801 mg.

The results of study 19-VIN-0275 with 801 mg formulation can be extrapolated to other strengths 267 mg and 534 mg, 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	Drug-induced liver injury (DILI) Photosensitivity reaction and rah Gastrointestinal symptoms
Important potential risks	Severe skin reactions
Missing information	QT prolongation Underlying specific cardiac events

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

Table 15: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Drug-Induced Liver Injury (DILI)	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8. PL sections 2, 4 Additional risk minimisation measures: - Physician's Safety checklist	Routine pharmacovigilance activities only Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Photosensitivity reaction and rash	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8. PL sections 2 and 4 Additional risk minimisation measures: - Physician's Safety checklist	Routine pharmacovigilance activities only Additional pharmacovigilance activities: None
Important identified risk: Gastrointestinal symptoms	Routine risk minimisation measures: SmPC sections 4.2 and 4.8 PL sections 2 and 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities only Additional pharmacovigilance activities: None
Important potential risk: Severe skin reactions	Routine risk minimisation measures: SmPC sections 4.4, 4.8 PL sections 2, 4 Additional risk minimisation measures: - None	Routine pharmacovigilance activities only Additional pharmacovigilance activities: None
Missing information: QT prolongation	Routine risk minimisation measures: None Additional risk minimisation measures: - None	Routine pharmacovigilance activities only Additional pharmacovigilance activities: None
Missing information: Underlying specific cardiac events	Routine risk minimisation measures: None Additional risk minimisation measures: - None	Routine pharmacovigilance activities only Additional pharmacovigilance activities: None

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Pirfenidone (L04AX05). The bridging report submitted by the applicant has been found acceptable.

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 IPF. No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical 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, two-way crossover pivotal oral bioequivalence study. 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 Viatris met the protocol-defined criteria for bioequivalence when compared with the reference medicinal product Esbriet. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, $AUC_{0-\infty}$, 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, the CRO was inspected by relevant EU authorities (2016, MHRA) and more recently by the USFDA in 2022 and 2021 and WHO in 2018.

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 Viatris is favourable in the following indication:

Pirfenidone Viatris 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 Viatris 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 Viatris should contain the following key elements related to liver function, drug-induced liver injury and photosensitivity:

Liver function, drug-induced liver injury

- Pirfenidone Viatris is contraindicated in patients with severe hepatic impairment or end stage liver disease.
- Elevations of serum transaminases can occur during treatment with Pirfenidone Viatris.
- There is a need to monitor liver function tests prior to initiation of treatment with Pirfenidone Viatris 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 Viatris 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.