COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pirfenidon Vivanta 267 mg and 801 mg film-coated tablets

(pirfenidone)

NL/H/5434/001-002/DC

Date: 4 November 2022

This module reflects the scientific discussion for the approval of Pirfenidon Vivanta 267 mg and 801 mg film-coated tablets. The procedure was finalised at 22 June 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Pirfenidon Vivanta 267 mg and 801 mg film-coated tablets, from Vivanta Generics s.r.o.

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

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Esbriet 267 mg and 801 mg film-coated tablets which have been registered in the EEA by Roche Registration GmbH since 28 February 2011 via a centralised procedure (EMEA/H/C/002154).

The concerned member states (CMS) involved in this procedure were Cyprus, Denmark, Finland, Germany, Norway, Portugal, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Pirfenidon Vivanta 267 mg is a white, oval shaped, film coated tablet debossed with “M” on one side and “PF1” on the other side and contains as active substance 267 mg pirfenidone.
Pirfenidon Vivanta 801 mg is a white, oval shaped, film coated tablet debossed with “M” on one side and “PF3” on the other side and contains as active substance 801 mg pirfenidone.

The two tablet strengths are of different sizes.

The tablets are packed in HDPE (high-density polyethylene) bottles or PVC/Aclar-Aluminium blisters.

The excipients are:
Tablet core – microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, silica colloidal anhydrous and magnesium stearate;
Film coating – polyvinyl alcohol-part hydrolysed (E1203), titanium dioxide (E171), macrogol 4000 (E1521) and talc (E553b).

The tablet cores of the two strengths are fully dose proportional.

II.2 Drug Substance

The active substance is pirfenidone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or pale yellow crystalline powder and is freely soluble in dichloromethane and methanol, soluble in ethanol and practically insoluble in water. Pirfenidone exhibits polymorphism; the crystalline form is consistently produced by the manufacturer.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., except for the solubility specification which is adequately explained by the difference in solubility at different tested temperatures. Additional requirements for a specific impurity content, residuals solvents, microbial testing, and particle size distribution have been included. Studies showed that the manufacturing process consistently produces the same polymorphic form of the active substance and that there is no change in polymorphic forms during manufacturing or storage of the finished product. Batch analytical data demonstrating compliance with this specification have been provided for six full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 6 months. Based on the data submitted, a retest period could be granted of 12 months and it was justified to have no storage conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients is justified and their functions explained. The stability of the polymorphic form during manufacture and storage has been adequately

demonstrated. The main development studies regarded the characterisation of the reference product, formulation development and optimisation studies. The dissolution method has been adequately developed. *In vitro* dissolution testing was performed for the higher strength tablets, complementary to the bioequivalence study. This demonstrated similarity with the reference product. For the lower strength tablets, the biowaiver of additional strength is acceptable from a quality perspective. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is a standard process which involves sifting, dry mixing, wet granulation, drying, pre-lubrication, lubrication, compression, coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production scaled batches for each strength.

Control of excipients

Except for Opadry II White, the excipients used are of Ph.Eur. quality and the components of which Opadry II White consist are also of Ph.Eur. quality. The specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, identification of titanium dioxide, average mass, uniformity of dosage unit, water content, dissolution, related substances, assay and microbiological quality. The specifications for release and shelf-life were identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable ICH guidelines. The product is stable when exposed to light and humidity. No special storage conditions are needed. No out of specifications or up/downwards trends were seen under long term and accelerated conditions for all batches. On basis of the data submitted, a shelf life was granted of 36 months for the PVC/Aclar-Al blister packaging and the HDPE bottle. There was no indication from stability and stress studies that the drug product may be susceptible to deterioration. Hence, it is justified that no in-use stability studies were required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Pirfenidon Vivanta has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Pirfenidon Vivanta is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Esbriet which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pirfenidone is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Pirfenidon Vivanta 801 mg film-coated tablets (Vivanta Generics s.r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference product Esbriet 801 mg film-coated tablets (Roche Registration GmbH, Germany).

The choice of the EU reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the 267 mg and 801 mg strengths. A comparable *in vitro* dissolution profile was shown for the different strength tablets under three conditions. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH has requested a biowaiver for the 267 mg strength product. The following general requirements must be met where a waiver for additional strength is claimed: 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, 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, capsule shell, colour agents and flavours are not required to follow this rule), d) appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) or i) and iii) below apply to the strength used in the bioequivalence study and the strength for which a waiver is considered;

i) the amount of the active substance(s) is less than 5 % of the tablet core weight, the weight of the capsule content;
ii) the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed;
iii) the amount of a filler is changed to account for the change in amount of active substance.

The amounts of other core excipients or capsule content should be the same for the concerned strengths.

The manufacturing process of Pirfenidon Vivanta 267 mg and 801 mg film-coated tablets is the same and the ratio of excipients to the amount of active substance is the same for both strengths. Further, a comparable *in vitro* dissolution profile was shown for the different strength tablets under the three requested conditions. Dissolution of the 801 mg and 267 mg strength is comparable, as the conditions mentioned in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr*, section 4.1.6) were met. Finally, the AUC and C_{max} for pirfenidone is considered linear over the relevant dose range. Therefore, a biowaiver for the additional 267 mg strength, based on the bioequivalence data for the 801 mg strength, is considered acceptable.

Bioequivalence study

Design

An open label, balanced, randomised, two treatments, two sequences, two periods, two-way crossover, single dose bioequivalence study was carried out under fed conditions in 60 healthy male subjects, aged 18-55 years, with a Body Mass Index (BMI) ≥18.5 and ≤ 30.0 kg/m^2 with a body weight of at least 55 kg, who did not smoke. Water intake was not allowed for 1 hour

before dosing and 1 hour after dosing. Study treatments were administered orally in sitting posture and the participants remained in supine position for at least 4 hours after dosing. Each subject received a single dose (801 mg) of one of the two pirfenidone formulations. The tablet was orally administered with 240 ml water, 30 minutes after consumption of a high fat breakfast (consisting of French fries, chicken fry, egg fry, 2 bread slices with butter and whole milk), following an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose within 90 minutes prior to drug administration and post dose at 00.17, 00.33, 00.50, 00.75, 01.00, 01.33, 01.67, 02.00, 02.33, 02.67, 03.00, 03.50, 04.00, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00 and 24.00 hours after administration of the products.

A single dose using the highest strength pirfenidone 801 mg tablet is appropriate to support the application of the product according to the bioequivalence guideline. Dosing under fed conditions is justified as the immediate release formulation should be taken with food only. Plasma AUC of pirfenidone increased in a dose-proportional manner. Therefore the use of the highest strength for demonstration of bioequivalence is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The reasons for re-analysis are acceptable and were prespecified in the protocol. The original and re-analysed values were provided and the repeated values were the ones reported and used in pharmacokinetic analysis. Based on the initial and repeated analyses, the reproducibility of the results is considered acceptable. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject was withdrawn from the study due to occurrence of an adverse event (vomiting) in period II. Three subjects had laboratory values outside normal ranges at check-in in period II. One study subject was absent in period II due to personal reasons. Therefore, a total of 55 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pirfenidone under fed conditions.

Treatment N=55	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	54699 ± 16390	55401 ± 16582	10005 ± 3148	1.67 (0.33-5.00)	2.91 ± 0.66
Reference	55767 ± 18698	56523 ± 19069	10316 ± 4188	1.67 (0.33-6.00)	2.90 ± 0.78
***Ratio (90% CI)**	0.99 (0.95 – 1.03)	--	0.99 (0.90 – 1.08)	--	--

CV (%)	13.1	--	28.4	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Pirfenidon Vivanta 801 mg film-coated tablets is considered bioequivalent with Esbriet 801 mg film-coated tablets.

The results of the study with 801 mg formulation can be extrapolated to other strength 267 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Pirfenidon Vivanta.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Photosensitivity reaction and rash • Drug induced liver injury (DILI) • GI symptoms
Important potential risks	• Severe skin reactions
Missing information	• QT prolongation • Underlying specific cardiac events

Routine risk minimisation measures are in place and additional risk minimisation measures have been accepted, which are in line with those of Esbriet. Objectives of the additional risk minimisation activity are 1) to inform healthcare professionals about the risks of photosensitivity reaction, rash and hepatic related events including asymptomatic abnormal levels of ALT/AST associated with pirfenidone and 2) to inform healthcare professionals about appropriate management of the risks to minimise its occurrence and its severity.

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 adverse drug reactions of special interest including photosensitivity reactions and skin rashes, abnormal liver function tests, drug-induced liver injury and any other clinically significant adverse drug reaction based on the judgment of the prescriber.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Esbriet. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report in which the PL of Pirfenidon Vivanta film-coated tablets is compared to the PL of Esbriet film-coated tablets (EMEA/H/C/002154) regarding the text and safety issues and compared to the PL of Rosuvastatine Vivanta (NL/H/4158/001-004) regarding the design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pirfenidon Vivanta 267 mg and 801 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Esbriet 267 mg and 801 mg film-coated tablets. Esbriet is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pirfenidon Vivanta with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 June 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N/A	N/A	N/A	N/A	N/A	N/A