LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pirfenidon Medical Valley (pirfenidone)

SE/H/2357/01-03/DC

This module reflects the scientific discussion for the approval of Pirfenidon Medical Valley. The procedure was finalised on 2023-09-13. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Pirfenidon Medical Valley, 267 mg, 534 mg, 801 mg, Film-coated tablet.

The active substance is pirfenidone. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Pirfenidon Medical Valley, 267 mg, 534 mg, 801 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant, Laboratorios Liconsa S.A., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, DK, IS, NL, NO and PL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Esbriet Capsule, hard 267 mg authorised in the Union since 2011, with Roche Registration GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Esbriet, 801 mg, Film-coated tablet from DE with Roche Registration GmbH as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of pirfenidone are well known. As pirfenidone is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Pirfenidon Medical Valley is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Pirfenidon Medical Valley from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Pirfenidon Medical Valley (Pirfenidone) with the reference product Esbriet.

Pharmacokinetic properties of the active substance
Absorption
The SmPC of the reference product recommends intake in fed state to minimise the risk of nausea and dizziness.

Linearity
Linear pharmacokinetics has been demonstrated following single-dose oral administration of 200-600 mg pirfenidone. No deviation from dose-proportional pharmacokinetics has been observed over the dose range 801-4005 mg/day under steady-state conditions.

Elimination
Following single dose administration of pirfenidone in healthy older adults, the mean apparent terminal elimination half-life was approximately 2.4 hours.

Study 19-VIN-0275
Methods
This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Pirfenidone, 801 mg, film-coated tablet with Esbriet, 801 mg, film-coated tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of pirfenidone were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 28 February 2020 and 09 March 2020.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for pirfenidone, n=54.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**45002 ± 15213**	**10818 ± 3397**	**1.750 (0.25 - 6.00)**
Reference	**40971 ± 11086**	**10054 ± 2599**	**1.875 (0.50 - 4.50)**
***Ratio (90% CI)**	**107.19 (102.06 - 112.57)**	**105.53 (98.96 - 112.53)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 267 mg and 534 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) and the draft Pirfenidone product-specific bioequivalence guidance (EMA/CHMP/901584/2022). The bioanalytical method was adequately validated.

Absence of studies with the additional strengths of 267 mg and 534 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) are fulfilled and the pharmacokinetics of pirfenidone is linear.

Based on the submitted bioequivalence study, Pirfenidon Medical Valley is considered bioequivalent with Esbriet.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. This is acceptable, as bioequivalence with the originator product has been demonstrated.

Risk Management Plan
The applicant 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 Medical Valley.

Part II Safety specification
In the submitted RMP (version 0.2, dated 11 May 2023), the following summary of safety concerns are proposed.

Summary of safety concerns	
Important identified risks	• Photosensitivity reaction and rash • DILI
Important potential risks	• None
Missing information	• None

DILI: drug-induced liver injury

The proposed safety concerns are aligned with those listed in the RMP of the reference product. Hence, the summary of safety concerns is acceptable.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested, including a guided questionnaire for assessment of drug-induced liver injury. No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
The applicant proposes additional risk minimization measures; i.e. safety checklists concerning liver function (drug-induced liver injury) and photosensitivity, with the objective to minimize the occurrence of these ADRs and to encourage the prescribers to report clinically-significant ADRs of "photosensitivity reaction and rash" and "Drug-Induced Liver Injury.
This is in accordance with the reference product and is thus endorsed.

Part VI Summary of the RMP
The applicant has adequately summarized the RMP.

Assessor´s Overall summary and Conclusion on the proposed RMP:
The submitted Risk Management Plan, version 0.2, dated 11 May 2023, is aligned with the RMP of the reference product Esbriet and is thus found acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Spanish.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Pirfenidon Medical Valley, is found adequate.

There were no objections to approval of Pirfenidon Medical Valley, from a non-clinical and clinical point of view.

Bioequivalence between the test and reference product has been adequately demonstrated.

The product information is acceptable.

The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

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

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

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

Liver function, drug-induced liver injury

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

VII. APPROVAL

The decentralised procedure for Pirfenidon Medical Valley, 267 mg, 534 mg, 801 mg, Film-coated tablet was positively finalised on 2023-09-13.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se