LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pirfenidon Cipla
(pirfenidone)

SE/H/2313/01-02/DC

This module reflects the scientific discussion for the approval of Pirfenidon Cipla. The procedure was finalised on 2023-11-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Pirfenidon Cipla, 267 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 Cipla, 267 mg, 801 mg, film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BE, DE, ES, FI, FR, IE, IT, NO, 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, 267 mg, hard capsule authorised in the Union since 2011-02-28, with Roche Registration GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Esbriet, 801 mg, film-coated tablet from Germany 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 the following medicinal products have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU: EU/3/07/491, EU/3/10/802, EU/3/12/1020, EU/3/14/1301, EU/3/14/1362, EU/3/16/1692, EU/3/18/2056, EU/3/18/2069, EU/3/22/2588, EU/3/22/2619, EU/3/22/2630, EU/3/22/2735.

The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant should submit a report on similarity (Module 1.7.1) and, if applicable, submit the data to support derogation from orphan market exclusivity (Module 1.7.2).

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 Cipla 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 Cipla from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one (1) bioequivalence study comparing Pirfenidon Cipla (Pirfenidone), 801 mg, film-coated tablets with the reference product Esbriet.

Pharmacokinetic properties of the active substance
Absorption: The absolute bioavailability of pirfenidone has not been determined in humans. Following a single dose of 801 mg pirfenidone with food, maximal plasma concentrations occur at approximately 3.5 hours.

Although concomitant food intake decreases the C_{max} by 50% and AUC by 15-20 %, the SmPC of the originator recommends that the product is administered with food for tolerability reasons. A reduced incidence of adverse events (nausea and dizziness) has been observed in fed subjects when compared to a fasted group. Thus, it is recommended that pirfenidone be administered with food to reduce the incidence 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: The terminal half-life is 2.4 hours.

Study 21-04-082
Methods

This was an open label, randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 54 healthy volunteers, comparing Pirfenidone, 801 mg, film-coated tablets with Esbriet, 801 mg, film-coated tablets 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 an 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 16 February 2022 and 24 February 2022.

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	**57919 ± 23939**	**10197 ± 2605**	**2.67 (1.00-4.50)**
Reference	**56319 ± 22312**	**10297 ± 3448**	**2.33 (0.50-5.00)**
***Ratio (90% CI)**	**102.49 (97.81 - 107.40)**	**100.73 (94.51 - 107.37)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to 24 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 strength of 267 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 strength of 267 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 since the pharmacokinetics of pirfenidone is linear over the therapeutic dose range.

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

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Cipla.

Safety specification
The MAH has submitted the version 0.3 RMP dated 16.10.2023 and proposed the following summary safety concerns:

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 RMP for Pirfenidon Cipla is in line with that of the reference product (Esbriet).

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and in accordance with the originator the applicant has proposed follow-up questionnaires concerning Drug induced liver injury (DILI), which is acknowledged. No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
aRMM is proposed, safety checklists concerning liver function and drug-induced liver injury (DILI) and photosensitivity. This is in accordance with the reference product and endorsed.
The information in annex 6 of the RMP is in line with the reference product.

Part VI Summary of the RMP
The summary of the RMP is acceptable.

Conclusion of RMP assessment
The submitted Risk Management Plan, version 0.3 RMP dated 16.10.2023 is acceptable.

The 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 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 English.

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 Cipla, is found adequate. There are no objections to approval of Pirfenidon Cipla, 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 conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

Additional risk minimisation measures (including educational material)

The SmPC and PL should be provided to all prescribers, along with the safety checklists, in line with the conditions stated in Annex IID in the EPAR for Esbriet. See IV Clinical aspects - Risk Management Plan - Risk minimisation measures.

Key elements as per Annex 6 are in line with the reference:

The MAH must ensure that at launch all physicians who are expected to prescribe <invented name> are provided
with a physician information pack containing the following:
● Product information (SPC)
● Physician information (safety checklists)
● Patient information (PIL)

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

Liver function, drug-induced liver injury
● <invented name> is contraindicated in patients with severe hepatic impairment or end stage liver disease.
● Elevations of serum transaminases can occur during treatment with <invented name>.
● There is a need to monitor liver function tests prior to initiation of treatment with <invented name> 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 <invented name> 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 Cipla, 267 mg, 801 mg, film-coated tablet was positively finalised on 2023-11-21.

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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)

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