LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pirfenidone Newbury
(pirfenidone)

SE/H/2230/01-02/DC

This module reflects the scientific discussion for the approval of Pirfenidone Newbury. The procedure was finalised on 2023-02-09. 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 Pirfenidone Newbury, 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 Pirfenidone Newbury, 267 mg and 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 DK and NO 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 and 801 mg respectively, film-coated tablet, authorised in EU 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 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 Orphan Designation Number:	EU/3/18/2056
EU Orphan Designation Number:	EU/3/14/1362
EU Orphan Designation Number:	EU/3/10/802
EU Orphan Designation Number:	EU/3/16/1692
EU Orphan Designation Number:	EU/3/15/1550
EU Orphan Designation Number:	EU/3/20/2309
EU Orphan Designation Number:	EU/3/14/1301
EU Orphan Designation Number:	EU/3/07/491
EU Orphan Designation Number:	EU/3/09/707
EU Orphan Designation Number:	EU/3/12/1020
EU Orphan Designation Number:	EU/3/18/2069

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 Pirfenidone Newbury 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 Pirfenidone Newbury 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 Pirfenidone Newbury with the reference product Esbriet.

Study 20-VIN-0191
Methods
This was a single-dose, two-way crossover study conducted in 62 healthy volunteers (52 completed), 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 18 Aug 2020 and 25 Aug 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=52.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**49018.4 ± 17290.4**	**10350.7 ± 2564.1**	**1.500 (0.25-4.50)**
Reference	**50545.3 ± 19142.3**	**11495.5 ± 3374.1**	**1.750 (0.50-4.50)**
***Ratio (90% CI)**	**99.29 (94.31-104.52)**	**91.87 (85.05-99.24)**	**-**

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 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 PKWP Q&A 4.13 on bioequivalence requirements for pirfenidone formulations. 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 considered linear over the relevant dose range.

Based on the submitted bioequivalence study, Pirfenidone Newbury film-coated tablet 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 Pirfenidone Newbury.

Safety specification
The MAH has submitted the version 0.4 RMP dated 2023-01-23 and proposed the following summary of safety concerns.

List of important risks and missing information	
Important identified risks	• Photosensitivity reaction and rash • DILI • Gastrointestinal symptoms
Important potential risks	• Severe skin reactions • Risk of medication error in patients transferring between capsules and tablets
Missing information	• QT Prolongation • Underlying specific cardiac events

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation measures is suggested, and aRMM concerning DILI and Photosensitivity reaction and rash are proposed. Please refer to section VIII.3 proposed list of conditions pursuant to Article 21a or specific obligations pursuant to article 22 of Directive 2001/83/EC in this Overview for the key elements of the aRMM.

Summary of the RMP
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. The submitted Risk Management Plan, version 0.4 signed 2023-01-23 is considered acceptable.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Esbriet 267 mg, 534 mg and 801 mg film-coated tablets, EMEA/H/C/002154 (content) and Etoricoxib 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets, EL/H/0198/001, EL/H/0198/002, EL/H/0198/003, EL/H/0198/004 (layout).

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Pirfenidone Newbury, is found adequate. There are no objections to approval of Pirfenidone Newbury, 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 educational material should contain the following key elements:

The MAH must ensure that at launch all physicians who are expected to prescribe Pirfenidone Newbury 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 Newbury should contain the following key elements related to liver function, drug-induced liver injury and photosensitivity:

Liver function, drug-induced liver injury

- Pirfenidone Newbury is contraindicated in patients with severe hepatic impairment or end stage liver disease.
- Elevations of serum transaminases can occur during treatment with Pirfenidone Newbury
- There is a need to monitor liver function tests prior to initiation of treatment with Pirfenidone Newbury 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 Newbury 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 Pirfenidone Newbury, 267 mg, 801 mg, Film-coated tablet was positively finalised on 2023-02-09.

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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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