LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pirfenidone Glenmark
(pirfenidone)

SE/H/2713/001-002/DC

This module reflects the scientific discussion for the approval of Pirfenidone Glenmark. The procedure was finalised at 2026-03-18. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Pirfenidone Glenmark, 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.

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: Immunosuppressants, other immunosuppressants, ATC code: L04AX05

Pirfenidone Glenmark is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF). The mechanism of action of pirfenidone has not been fully established. However, existing data suggest that pirfenidone exerts both antifibrotic and anti-inflammatory properties in a variety of in vitro systems and animal models of pulmonary fibrosis (bleomycin- and transplant-induced fibrosis).

Treatment with Pirfenidone Glenmark should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of IPF.

The applied indications for the submitted product are the same as authorised for the reference product.

II.2 General comments on the submitted dossier

The application for Pirfenidone Glenmark, 267 mg, 801 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI, DE, NL, NO, ES, IT 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, capsule, hard 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 Germany with Roche Registration GmbH as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with

which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance, a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU. The declaration is acceptable.

GCP
A statement on the application of appropriate GCP standards in the submitted study has been provided. No issues regarding GCP have been identified.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The applicant has submitted an ERA-document for the generic medicinal product Pirfenidone.

This Marketing Authorization is based on Article 10(1) of Directive 2001/83/EC (generic medicinal

product). Pirfenidone 267 mg | 801 mg film-coated tablets is a generic formulation similar to the reference product Esbriet 267 mg | 801 mg, manufactured by Roche Registration GmbH.

Pirfenidone 267 mg | 801 mg film-coated tablets is indicated in adults for the treatment of idiopathic pulmonary fibrosis. Upon initiating treatment, the dose should be titrated to the recommended daily dose of 2403 mg/day over a 14-day period.

The active substance is pirfenidone, which is a pyridone that is 2-pyridone substituted at positions 1 and 5 by phenyl and methyl groups respectively (PubChem 2025). The mechanism of action of pirfenidone has not been fully established. However, existing data suggest that pirfenidone exerts both antifibrotic and anti-inflammatory properties in a variety of in vitro systems and animal models of pulmonary fibrosis (bleomycin- and transplant-induced fibrosis). Pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors.

The active substance pirfenidone is not an antibiotic, antiparasitic or endocrine active substance (EAS).

Risk Assessment
The Phase I risk assessment is performed based on a decision tree, as detailed in the current ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr).

Pirfenidone is not a naturally occurring substance nor a non-natural peptide/protein.

The applicant identified an earlier ERA for the reference medicinal product Esbriet (Esbriet EPAR, EMEA/H/C/002154/II/0074) and claims that the scientific conclusions reached are applicable to the current generic product. A letter of access to ERA studies was requested from the MAH of Esbriet, which was refused. However, repetition of ERA studies will generally not be required as the ERA for Esbriet was considered satisfactory by the CHMP. The most recent ERA for Esbriet was performed in 2023 and includes risk assessments for all environmental compartments that are mandatory under the new guideline i.e. surface water, sewage treatment plant functioning and sediment. This approach is agreed.

According to the EPAR of Esbriet, the refined PEC(sw) was above the action limit of 0.01 µg/L, triggering phase IIa risk assessment. For phase IIa risk assessment, data from studies OECD 106, 301, 308, 201, 211, 210, 209, and 218 were available, with the conclusion that a risk to the sewage treatment plant, surface water, groundwater, sediment and terrestrial compartment is not anticipated.

The applicant argues that since Pirfenidone 267 mg | 801 mg film-coated tablets is a generic formulation of Esbriet, the therapeutic indication and posology are the same and an increase in environmental exposure is not expected, no new indication nor a new patient population is added, the maximum daily dose is not increased, no new route of administration nor new pharmaceutical form is added, and the marketing authorization is not applied in a member state with a higher prevalence of the disease. Therefore, the Applicant’s view is that PEC values of Esbriet determined for the different environmental compartments are applicable for the concerned product. In addition, the refined Fpen based on prevalence is not expected to have changed markedly since the previous ERA performed in 2023.

PBT/vPvB screening
The experimental octanol-water partition coefficient (Log Kow) of pirfenidone calculated as mean value of six determinations, according to OECD guideline 107 was 1.21, 1.22 and 1.22 for pH 5.0, 7.0 and 9.0, respectively. This is below the trigger value of 4.5; therefore, pirfenidone is considered not to

be PBT, nor vPvB.

Conclusion

The ERA stops in Phase I. A Phase II environmental assessment is not required as according to the Phase I decision tree, question 2a/b/c/d, possible environmental risks for pirfenidone have already been sufficiently assessed in the authorization procedure for the medicinal product *Esbriet.* Pirfenidone is not expected to pose a risk to the environment.

There are no objections to approval of Pirfenidone 267 mg, 801 mg film-coated tablets from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Pirfenidone Glenmark with the reference product Esbriet.

Pharmacokinetic properties of the active substance
Absorption:
Bioequivalence was demonstrated in the fasted state when comparing an 801 mg tablet to three 267 mg capsules. In the fed state, the 801 mg tablet met bioequivalence criteria based on the AUC measurements compared to the capsules, while the 90% confidence intervals for C_{max} (108.26% - 125.60%) slightly exceeded the upper bound of standard bioequivalence limit (90% CI: 80.00% - 125.00%). The effect of food on pirfenidone oral AUC was consistent between the tablet and capsule formulations. Compared to the fasted state, administration of either formulation with food reduced pirfenidone C_{max}, with pirfenidone tablet reducing the C_{max} slightly less (by 40%) than pirfenidone capsules (by 50%). A reduced incidence of adverse events (nausea and dizziness) was observed in fed subjects when compared to the fasted group. Therefore, it is recommended that pirfenidone be administered with food to reduce the incidence of nausea and dizziness.

The absolute bioavailability of pirfenidone has not been determined in humans.

Linearity:
Linear pharmacokinetics have been demonstrated following single-dose oral administration of 200-600 mg pirfenidone[1]. In the Marketing Authorisation Application (MAA) for the originator capsule, no significant dose dependency was identified suggesting linear pharmacokinetics up to a dose of 600 mg three time daily (EPAR Esbriet). In addition, PKWP has reviewed the data from the submitted dossier for the originator capsule and considers deviation from dose-proportional pharmacokinetics has not been observed over the dose range 801-4005 mg/day under steady-state conditions.

Linearity of pharmacokinetics was also assessed by the CHMP in the line extension application for the originator film-coated tablets. Therefore, considering the data available in the dossiers for the originator capsule and film-coated tablets, and for a substance with poor solubility and dose proportional or more than dose proportional pharmacokinetics, a bioequivalence study with the highest strength, i.e. 801 mg, is advised.

[1] Huang NY, Ding L, Wang J, Zhang QY, Liu X, Lin HD, Hua WY. Pharmacokinetics, safety and tolerability of pirfenidone and its major metabolite after single and multiple oral doses in healthy Chinese subjects under fed conditions. Drug Res (Stuttg). 2013 Aug;63(8):388-95. doi: 10.1055/s-0033-1341478. Epub 2013 Apr 11. PMID: 23580109.

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

Study GRC-BS-105-23
Methods
This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Pirfenidone Glenmark, 801 mg, filmcoated tablets with Esbriet, 801 mg, filmcoated 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 27 June 2024 and 5 July 2024.

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=58.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**66659.18 ± 27191.02**	**12006.83 ± 2727.03**	**2.00 (0.50 – 5.00)**
Reference	**66473.46 ± 28708.79**	**11568.31 ± 2984.03**	**2.00 (0.50 – 5.00)**
***Ratio (90% CI)**	**101.27 (95.71- 107.16)**	**104.86 (99.37- 110.66)**	**-**
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), ICH M13A, the PKWP Q&A 4.13 on bioequivalence requirements for pirfenidone formulations and the Pirfenidone product-specific bioequivalence guidance (EMA/CHMP/901584/2022). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Pirfenidone Glenmark 810 mg film-coated tablets are considered bioequivalent with Esbriet 810 mg film-coated tablets.
Absence of studies with the additional strength of 267 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and linear pharmacokinetics has been demonstrated following single-dose oral administration of 200–600 mg pirfenidone while no deviation from dose-proportional pharmacokinetics has been observed over the dose range 801–4005 mg/day under steady-state conditions.

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.

Pharmacovigilance system
Proposed MAH: [Glenmark Arzneimittel GmbH]

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Glenmark.

Part II Safety specification

Table 1: Summary of Safety Concerns

Important identified risk(s)	• Photosensitivity reaction and rash • Drug induced liver injury
Important potential risk(s)	• None
Missing information	• None

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

Part V Risk minimisation measures
Additional risk minimization measures are proposed, a safety checklist concerning liver function, drug-induced liver injury and photosensitivity. This is in accordance with the reference product and endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version V0.2 signed 2025-10-07 is considered 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.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Pirfenidone Glenmark, is found adequate. There are no objections to approval of Pirfenidone Glenmark, 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.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 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 Glenmark are provided with a physician information pack containing the following:
● Product information (SPC)
● Physician information (safety checklists)
● Patient information (PIL)

The educational material should contain the following key elements: related to liver function, drug-induced liver injury and photosensitivity:
Details of proposed additional risk minimisation activities (if applicable).

Draft key messages of the additional risk minimisation measures
Before initiating Pirfenidone, and in addition to reading the Summary of Product Characteristics, please check each of the following:

Drug-induced Liver Injury
Prior to initiation of treatment:

- The patient does not have severe hepatic impairment or end stage liver disease. Pirfenidone is contraindicated in patients with severe hepatic impairment or end stage liver disease
- Liver function tests have been performed prior to initiation of treatment with Pirfenidone
- I am aware that elevations of serum transaminases can occur during treatment with Pirfenidone
- The patient is informed that serious liver injury may occur and that he/she should contact their prescribing physician or regular physician immediately for clinical evaluation and liver function tests if symptoms of liver injury including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice (as described in the patient information leaflet) occur.

During treatment:

- Liver function tests will be performed monthly in the first six months of treatment
- Liver function tests will be performed every three months thereafter during treatment
- Patients who develop liver enzyme elevations will be closely monitored and the dose of Pirfenidone will be adjusted or treatment will be permanently discontinued if necessary (please refer to the Summary of Product Characteristics for recommendations)
- Prompt clinical evaluation and liver function tests will be performed if a patient develops symptoms or signs of liver injury (please refer to the Summary of Product Characteristics for recommendations).

Photosensitivity

- The patient is informed that Pirfenidone is known to be associated with photosensitivity reactions and that preventive measures have to be taken
- The patient is advised to avoid or reduce exposure to direct sunlight (including sunlamps).
- The patient is instructed to use a sunblock daily, to wear clothing that protects against sun exposure, and to avoid other medications known to cause photosensitivity.
- The patient is informed that he/she should report to the prescribing physician or regular physician if any new and significant skin rash occurs.

Reporting of adverse events
Healthcare professionals should report any adverse events suspected to be associated with the use of Pirfenidone according to national reporting requirements.
If you are aware of any suspected adverse reactions associated with the use of Pirfenidone, including clinically significant photosensitivity reactions and skin rashes, drug-induced liver injury, clinically significant abnormal liver function tests and any other clinically significant ADRs, please report such information to <<<Affiliate Address and Contact details>>>>>

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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 EMEA/H/C/002154 and Atovaquone NL/H/3762/001/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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