LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nintedanib Glenmark
(nintedanib esilate, nintedanib)

SE/H/2495/01-02/DC

This module reflects the scientific discussion for the approval of Nintedanib Glenmark. The procedure was finalised at 2025-12-22. 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

TABLE OF CONTENTS

I. Introduction 3
II. Executive summary 3
II.1 About the product 3
II.2 General comments on the submitted dossier 3
II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles 3
III. Scientific OVERVIEW AND DISCUSSION 4
III.1 Quality aspects 4
III.2 Non-clinical aspects 4
III.3 Clinical aspects 5
IV. BENEFIT RISK ASSESSMENT 8
V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION 9
V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC 9
V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC 9
V.3 Summary of Product Characteristics (SmPC) 9
V.4 Package Leaflet (PL) 9
V.4.1 Package Leaflet 9
V.4.2 Assessment of User Testing 9
VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY 10

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Nintedanib Glenmark, 100 mg, 150 mg, Capsule, soft.

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

II. EXECUTIVE SUMMARY

II.1 About the product

Nintedanib is a small molecule receptor tyrosine kinase inhibitor (TKI) blocking vascular endothelial growth factor receptors (VEGFR 1-3), fibroblast growth factor receptors (FGFR 1-3) and platelet-derived growth factor receptors (PDGFR) α and β kinase activity in the low nanomolar range.

Nintedanib binds competitively to the ATP binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation, migration and fibroblast to myofibroblast transformation of lung fibroblasts. In addition, Flt-3, Lck and Src kinases are inhibited by nintedanib.

The inhibition of signalling pathways of several tyrosine kinases; vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) involved in lung fibrosis is expected to reduce progressive fibrosis and fibroblast foci with interspersed areas of lung sparing and minimal excess inflammatory infiltrate in idiopathic pulmonary fibrosis (IPF).

II.2 General comments on the submitted dossier

The application for Nintedanib Glenmark, 100 mg, 150 mg, capsule, soft, 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 CZ, DE, DK, ES, FI, IT, NL, NO and UK(NI) as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Ofev, 100 mg, capsule, soft, authorised in EU since 2015, with Boehringer Ingelheim International GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Ofev, 150 mg, capsule, soft, from Germany with Boehringer Ingelheim International 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.

GCP aspects
A statement on the application of appropriate GCP standards in the submitted study has been provided. No issues regarding GCP have been identified. The clinical and the bioanalytical facilities were inspected by the FDA in 2019, 2022 and 2023, without any critical findings. No inspection of the submitted bioequivalence study is needed.

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 nintedanib are well known. As nintedanib 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)
Since Nintedanib Glenmark 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 Nintedanib Glenmark 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 Nintedanib Glenmark with the reference product Ofev.

Pharmacokinetic properties of the active substance
Nintedanib reached maximum plasma concentrations approximately 2-4 h after oral administration as soft gelatine capsule under fed conditions (range 0.5-8 h). The absolute bioavailability of a 100 mg dose was 4.69% (90% CI: 3.615-6.078) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism. Nintedanib exposure increased dose-proportionally in the dose range of 50-450 mg once daily and 150-300 mg twice daily. Steady state plasma concentrations were achieved within one week of dosing at the latest.

After food intake, nintedanib exposure increased by approximately 20% compared to administration under fasted conditions (CI: 95.3-152.5%) and absorption was delayed (median t_{max} fasted: 2.00 h; fed: 3.98 h).

The pharmacokinetics of nintedanib can be considered linear with respect to time (i.e. single-dose data can be extrapolated to multiple-dose data). Accumulation upon multiple administrations was 1.04-fold for C_{max} and 1.38-fold for AUC_{τ}. Nintedanib trough concentrations remained stable for more than one year.

The terminal half-life of nintedanib was between 10 and 15 h.

Study GRC-BS-047-23
Methods
This was a single-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Nintedanib, 150 mg, capsule, soft, with Ofev, 150 mg, capsule, soft, under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of nintedanib were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 10th August 2023 and 9th September 2023.

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 nintedanib, n=38.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**341.67 ± 126.48**	**44.09 ± 18.54**	**4.25 (1.33 – 6.50)**
Reference	**359.54 ± 135.40**	**46.88 ± 20.93**	**4.50 (1.67 – 6.00)**
***Ratio (90% CI)**	**92.91 (85.19 – 101.32)**	**93.89 (86.38 – 102.05)**	**-**

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 100 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). As the SmPC of the reference product recommends administration with food a study in the fed state is appropriate. The bioanalytical method was adequately validated.

Based on the submitted bioequivalence study, Nintedanib Glenmark is considered bioequivalent with Ofev.

Absence of studies with the additional strength of 100 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) are fulfilled and since the pharmacokinetics of nintedanib is linear between 100 mg and 150 mg.

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

Pharmacovigilance system
Proposed MAH (RMS and CMS DE, DK, ES, FI, NL, NO, UK(NI)): *Glenmark Arzneimittel GmbH*;
Proposed MAH (CMS CZ, IT): *Glenmark Pharmaceuticals s.r.o.*:
The Applicant has submitted a revised signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System (Glenmark). 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 Nintedanib Glenmark.

Part II Safety specification
The proposed Summary of safety concerns (RMP Part II: Module SVIII) is included below.
It is aligned with the reference product RMP and is thus endorsed.

Important identified risks	DILI
	Bleeding
	Myocardial infarction
	Weight decreased in paediatric population
Important potential risks	Venous thromboembolism
	Arterial thromboembolism excluding myocardial infarction
	Perforation
	Hepatic failure
	Effect on bone development and growth in paediatric population
	Effect on tooth development disorders in paediatric population
Missing information	Treatment of SSc-ILD patients with pulmonary hypertension

Part III Pharmacovigilance Plan
The required routine pharmacovigilance activities (including adverse drug reaction reporting, signal detection, submission of expedited adverse drug reaction reports and Periodic Safety Update Reports etc.) will be performed by the company as agreed in the RMP and in any subsequent updates of the RMP.

No activities beyond routine pharmacovigilance activities are required for nintedanib. Nevertheless, in addition to routine pharmacovigilance activities, the following specific adverse reaction follow-up questionnaires are proposed by the applicant to further identify the risks of nintedanib:

Important identified risks
- DILI (restricted to serious events of liver enzyme increases, DILI, and hepatic failure)
- Myocardial infarction (Note: one follow-up questionnaire for all arterial thromboembolism events)
- Bleeding (defined as serious according to GVP, assessed as serious by reporter, listed in important medical events list or initial case without enough information for assessment of seriousness)

Important potential risks
- Arterial thromboembolism excluding myocardial infarction (note: one follow up questionnaire for all arterial thromboembolism events)
- Perforation
- Hepatic failure
- Effect on bone development and growth in paediatric population
- Effect on tooth development disorders in paediatric population

Part V Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The applicant has adequately summarised the RMP. The Summary of the RMP is endorsed.

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.
The submitted Risk Management Plan, version 0.2, signed 4 December 2025, 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, Nintedanib Glenmark, is found adequate. There are no objections to approval of Nintedanib 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

Post approval commitments
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)**

N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

N/A

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 Ofev soft capsules (EMEA/H/C/003821) for the content of the PL, and to Atovaquone oral suspension/ Dipyridamole modified release capsules/ Hydrocotisone tablets (NL/H/3762/001/DC; NL/H/4294/001/DC; UK/H/6924/001-003/DC) for the layout of the PL.

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
-	-	-	-	-	-