LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nintedanib Eignapharma
(nintedanib esilate)

SE/H/2390/01-02/DC

This module reflects the scientific discussion for the approval of Nintedanib Eignapharma. The procedure was finalised on 2024-06-19. 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 Nintedanib Eignapharma, 100 mg, 150 mg, Capsule, soft.

The active substance is nintedanib, nintedanib esilate. 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 Nintedanib Eignapharma, 100 mg, 150 mg, Capsule, soft, 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 DE, FR, IT and ES as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Vargatef, 100 mg, Capsule, soft authorised in the Union since 2014, with Boehringer Ingelheim International GmbH, Germany, as marketing authorisation holder.

The reference product used in the bioequivalence study is Ofev, 150 mg, Capsule, soft, from DE with Boehringer Ingelheim International GmbH, Germany as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

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 nintedanib are well known. As nintedanib 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 Nintedanib Eignapharma 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 the product from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study comparing Nintedanib Eignapharma (Nintedanib) with the reference product Ofev.

Pharmacokinetic properties of the active substance
Absorption:
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. Dose proportionality was shown by increase of nintedanib exposure (dose range 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).

Linearity:
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.

Elimination:
The terminal half-life of nintedanib was between 10 and 15 h (gCV % approximately 50%).

Study 0671-18
Methods
This was a single-dose, two-way crossover study conducted in 57 healthy volunteers (54 completed), comparing Nintedanib, 150 mg, soft capsule with Ofev, 150 mg, soft capsule under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 120 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 25 December 2018 and 12 January 2019.

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=54.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**548.2 ± 190.5**	**57.9 ± 25.7**	**4.250 (1.000 - 7.000)**
Reference	**556.5 ± 175.3**	**56.5 ± 21.1**	**5.500 (1.000 - 10.017**
***Ratio (90% CI)**	**97.6 (94.17 - 101.23)**	**100.3 (94.23 - 106.74)**	**-**
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 Eignapharma 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. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Nintedanib Eignapharma.

Part II. Safety specification

Important identified risks	• Drug-induced liver injury (DILI) • Bleeding • Myocardial infarction
Important potential risks	• Venous thromboembolism • Arterial thromboembolism excluding myocardial infarction • Perforation • Hepatic failure • Effect on bone development and growth if used off-label in paediatric patients <18 years-of-age • Effect on teeth development if used off-label in paediatric patients <18 years-of-age
Missing information	• Treatment of SSc-ILD patients with pulmonary hypertension

SSc-ILD = Systemic sclerosis associated interstitial lung disease

The proposed Summary of safety concerns complies with the RMP of the reference product Ofev, which is endorsed.

Part III. Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.
However, in accordance with the RMP of the reference product Ofev, follow-up questionnaires are proposed for some of the important identified/potential risks. This is endorsed.

Part V. Risk minimisation measures
The applicant concludes that the safety information in the proposed product information is aligned to the reference medicinal product; no additional risk minimisation activities are proposed, which is endorsed.

Part VI. Summary of the RMP
The proposed RMP for Nintedanib Eignapharma is adequately summarised by the applicant.

Conclusion of the RMP assessment
The submitted Risk Management Plan, version 1.1 signed 24 April 2024, 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.

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 Ofev soft capsules (EMEA/H/C/003821) and Zoledronic Acid Accord concentrate for solution for infusion (PT/H/0472/001/DC).
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, Nintedanib Eignapharma, is found adequate. There are no objections to approval of Nintedanib Eignapharma, 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

N/A

VII. APPROVAL

The decentralised procedure for Nintedanib Eignapharma, 100 mg, 150 mg, Capsule, soft was positively finalised on 2024-06-19.

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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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