COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nintedanib Tillomed 100 mg and 150 mg, soft capsules
(nintedanib esilate)

NL/H/6348/001-002/DC

Date: 22 April 2026

This module reflects the scientific discussion for the approval of Nintedanib Tillomed 100 mg and 150 mg, soft capsules. The procedure was finalised on 23 July 2025. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
ILDs	Interstitial Lung Diseases
IPF	Idiopathic Pulmonary Fibrosis
MAH	Marketing Authorisation Holder
PBT/vPvB	Persistent, Bioaccumulative, and Toxic/very Persistent and very Bioaccumulative
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
SSc-ILD	Systemic Sclerosis associated Interstitial Lung Disease
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Nintedanib Tillomed 100 mg and 150 mg, soft capsules, from Tillomed Malta Limited.

The product is indicated:

- in adults for the treatment of idiopathic pulmonary fibrosis (IPF)
- in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype
- in adults for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD)

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Ofev 100 mg and 150 mg, soft capsules, which has been registered by Boehringer Ingelheim International GmbH in the EEA via a centralised procedure (EU/1/14/979) since 15 January 2015.

The concerned member state (CMS) involved in this procedure was Germany.

II. QUALITY ASPECTS

II.1 Introduction

Nintedanib Tillomed 100 mg and 150 mg are soft capsules. The two strengths can be distinguished by colour and size and are as follows:

Nintedanib Tillomed 100 mg
Peach, opaque and oblong soft capsules with a size of approximately of 15.3 x 6.1 mm, containing as active substance 100 mg of nintedanib, as 120.4 mg of nintedanib esilate.

Nintedanib Tillomed 150 mg
Brown, opaque and oblong soft capsules with a size of approximately of 17.0 x 7.0 mm, containing as active substance 150 mg of nintedanib, as 180.6 mg of nintedanib esilate.

The excipients are:
Capsule fill - macrogol 400
Capsule shell - gelatin (E441), sorbitol (liquid, partially dehydrated) (E420), glycerol (E422), titanium dioxide (E171), ferric oxide red (E172) and ferric oxide yellow (E172).

The capsule content of the two capsule strengths is dose proportional.

The soft capsules are packed in polyethylene terephthalate/aluminium – polyamide/aluminium/polyvinyl chloride (PET/Alu - Polyamide/Alu/PVC) blisters.

II.2 Drug Substance

The drug substance is nintedanib esilate, an established substance not described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a solid, bright and yellow powder and practically insoluble in water. Nintedanib is an achiral molecule and shows a Z-isomer. For this product, the same polymorphic form is consistently produced.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of two branches that converge at the level of the intermediate. The introduction of the starting materials in the first branch of the synthesis is followed by chemical transformation steps with one isolated intermediate. The introduction of the starting materials in the second branch of the synthesis is followed by chemical transformation steps respectively and one isolated intermediate. The formation of the intermediate is subsequently followed by a purification step, salt formation step and milling step. No class 1 organic solvents are used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and is acceptable in view of the route of synthesis and the requirements of various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three production batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The soft capsules are manufactured using six major steps: gelatin mass preparation, fill suspension preparation, encapsulation, drying, visual inspection and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three production batches for each strength in accordance with the relevant European guidelines.

Control of excipients

The excipients, except for the iron oxides and a temporary excipient, comply with the Ph.Eur. requirements. These specifications are acceptable. Furthermore, the iron oxides comply with the purity criteria as laid down in EU Regulation 231/2012. In addition, the specification, analytical procedures, validation of analytical procedures and justification of specification of the temporary excipient are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes the check of all parameters relevant to this pharmaceutical form. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scale batches for each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production batches of each strength stored at 25°C/ 60% RH (36 months), at 30°C/ 65% RH (12 months) and at 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product. Photostability studies were performed in accordance with ICH recommendations. All results stayed within the proposed acceptance criteria. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are “Do not store above 25ºC. Store in the original package in order to protect from moisture.”

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for gelatin have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Nintedanib Tillomed has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Nintedanib Tillomed is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Ofev which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Nintedanib is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below. In addition, a biowaiver is requested for the lower 100 mg strength.

IV.2 Pharmacokinetics

The bioequivalence study was conducted in which the pharmacokinetic profile of the test product Nintedanib Tillomed 150 mg, soft capsules (Tillomed Malta Limited, Malta) was compared with the pharmacokinetic profile of the reference product Ofev 150 mg, soft capsules (Boehringer Ingelheim International GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements, according to the EMA Bioequivalence guideline are met for a waiver of the 100 mg strength:

a. the 100 mg and 150 mg capsules are manufactured by the same manufacturing process,
b. the qualitative composition of the 100 mg and 150 mg strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. Similarity of *in vitro* dissolution has been demonstrated at all conditions. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.
The lower limit of the 90% confidence interval of the expected-f_2 calculated by bootstrapping is applied for the comparison of the dissolution profiles in pH 4.5 and pH 6.8. The similarity of the dissolution profiles can be concluded. In addition, although similarity between the comparative dissolution profiles is observed with bootstrapping in pH 6.8, mathematical evaluation was not considered necessary due to the drug release of < 15% in 60 minutes. The conducted bootstrap methodology is acceptable according to the EMA guideline on the investigation of bioequivalence and the EMA Q&A 3.13.

Bioequivalence study

Study nr C1B01131

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, balanced, open label bioequivalence study was carried out under fed conditions in 120 healthy male subjects, aged 19-44 years old. Each subject received a single dose (150 mg) of one of the two nintedanib formulations. After an overnight fasting of at least 8 hours the subjects were served a standardised high-fat and high-calorie breakfast of 926 calories. The tablet was orally administered with 240 ml water 30 minutes after breakfast was served. There were two dosing periods, separated by a washout period of ten days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products. The design of the study is acceptable.

Nintedanib must be taken with reference to food intake. The capsules should be taken with food, swallowed whole with water, and should not be chewed. The capsule should not be opened or crushed. Therefore, a food interaction study is necessary. The bioequivalence study under fed conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Out of the 120 subjects, one subject did not report for subsequent period of the study, five subjects were withdrawn due to protocol violation, one subject withdrew for personal reasons and two subjects were withdrawn due to adverse events (vomiting). The remaining 111 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nintedanib, 150 mg under fed conditions.

Treatment N=111	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	324.63 ± 133.84	341 ± 142.19	39.04 ± 14.62	4.33 (1.50 – 6.00)
Reference	329.84 ± 131.08	346.87 ± 142.35	39.54 ± 14	4.33 (1.50 – 7.00)
***Ratio (90% CI)**	0.97 (0.93 – 1.01)	-	0.98 (0.94 – 1.02)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC0-t and Cmax are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nintedanib Tillomed 150 mg is considered bioequivalent with Ofev 150 mg.

The results of study nr. C1B01131 can be extrapolated to the other strength 100 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Tillomed. At the time of approval, the most recent version of the RMP was version 0.2 dated 20 February 2023.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Drug-induced liver injury (DILI) • Bleeding • Myocardial infarction
Important potential risks	• Venous thromboembolism • Arterial thromboembolism excluding myocardial infarction • Perforation • Hepatic failure
Missing information	• Treatment of SSc-ILD patients with pulmonary hypertension

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Ofev. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of: a pilot test with four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL 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

Nintedanib Tillomed 100 mg and 150 mg, soft capsules have a proven chemical-pharmaceutical quality and are generic forms of Ofev 100 mg and 150 mg, soft capsules. Ofev is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Nintedanib Tillomed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 July 2025.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/6348/001-2/IB/001	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation: Submission of Updated ERA according to the current ERA guidance EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*	Yes	3-11-2025	Approved	N.A.
NL/H/6348/001-2/IB/002	Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	No	25-11-2025	Approved	N.A.

Annex 1: - Submission of Updated Environmental Risk Assessment (NL/H/6348/001-002/IB/001)

I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the variation for Nintedanib Tillomed 100 mg and 150 mg (nintedanib esilate), in the treatment of:

- adults for the treatment of idiopathic pulmonary fibrosis (IPF)
- adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype
- adults for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD)

for the following proposed changes to update the Environmental Risk Assessment (ERA)

is not approvable unless the MAH can provide satisfactory responses to the request for supplementary information. The details of this request for supplementary information are provided in section IV.

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

The aim of this type IB variation is to update the Environmental Risk Assessment (ERA) for nintedanib esilate in accordance with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 Rev. 1 - Corr.*).

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

N/A

III.2 Non clinical aspects

III.2.1 Environmental risk assessment

III.2.1.1 ERA in the previous procedure - summary

Directive 2001/83/EC requires submission of an evaluation of the potential environmental risks posed by medicinal products in any new Marketing Authorisation Application (MAA). The European Medicines Agency (EMA) provides guidance on how to perform an Environmental Risk Assessment (ERA) of medicinal products for human use (EMA 2024).

The reference medicinal product Ofev (nintedanib 100 mg and 150 mg softgelatin capsules, by Boehringer Ingelheim) has already undergone a full Environmental Risk Assessment (ERA) as part of its marketing authorization. This implies that the environmental risks of nintedanib were evaluated and deemed acceptable by the EU authorities when Ofev was approved. In accordance with regulatory expectations, the MAH (Cinfa) formally requested access to the ERA data and full study reports from the Marketing Authorization Holder (MAH) of Ofev (Boehringer Ingelheim) in order to avoid unnecessary duplication of studies. However, Boehringer Ingelheim refused to provide the ERA information.

Therefore, an ERA for nintedanib has been conducted following the Phase I and PBT/vPvB (Persistent, Bioaccumulative, and Toxic/very Persistent and very Bioaccumulative) decision tree in the EMA guidance (2024). Section III.2.1.2 provides a summary of the findings.

III.2.1.2 Conclusion on ERA assessment

An ERA was prepared for a generic form of nintedanib based on the originator's product, Ofev, following the Phase I and PBT/vPvB decision tree in the EMA guidance (2024). The generic form will be marketed in the same dosage and form as the originator's product, for all the same disease indications. The MAH reached out to the originator (Boehringer Ingelheim) to purchase access to the ERA data, but the data sharing request was declined.

The previous ERAs reported a log KOW below the PBT/vPvB screening value of 4.5 for nintedanib. Therefore, nintedanib is not identified as a PBT/vPvB substance.

III.3 Clinical aspects

N/A

III.4 Product information

N/A

IV. OVERALL CONCLUSION

The MAH has submitted an ERA for their generic product containing the active substance nintedanib. No studies have been submitted, but a complete set of ERA studies was performed for the reference product Ofev (EMEA/H/C/003821). An email to the innovator asking for data sharing has been sent and included in the dossier. Unfortunately, the request was denied. A literature search has been conducted, but no relevant new information on ERA endpoints have been identified.
Although the MAH has adequately justified that the proposed generic product is identical in posology, patient population and indication, according to the revised guideline, the MAH should discuss whether the conclusions of the ERA are still relevant and in line with the revised guideline, and whether the ERA is complete and up to date. This assessment has been done by the assessor:

The risk for soil has not been addressed according to the revised guideline. It appears that the trigger is met, since the Kfoc,sludge > 1000. The MAH is requested to address this issue, provide the necessary studies for assessment and update the ERA accordingly. Alternatively, the MAH is asked to contact the ERA owner and initiate a consortium to fill this data gap and conclude on the risk to soil. The MAH is asked to provide a report documenting the initiative on organising consortia within one-year including a time table when the data for soil assessment will be available.

Conclusion on ERA assessment

The ERA is acceptable. A commitment has been made to initiate a consortium within a year to provide the missing data for soil assessment.