Medicines Evaluation Board

Public Assessment Report

Scientific discussion

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

NL/H/5730/001-002/DC

Date: 15 June 2026

This module reflects the scientific discussion for the approval of Nintedanib Hexal 100 mg and 150 mg, soft capsules. The procedure was finalised on 2 October 2024. 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
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
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 Hexal 100 mg and 150 mg, soft capsules, from Hexal AG.

The product is indicated in adults for treatment of:

- idiopathic pulmonary fibrosis (IPF)
- other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype
- 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 Hexal is a soft capsule. The two strengths can be distinguished by their colour and printing, as follows:

- The 100 mg strength are peach-coloured, opaque, oblong soft gelatin capsules, measuring 13.5 to 17.5 mm in length, containing yellow viscous suspension and are imprinted in red ink with “NT 100”.
- The 150 mg strength are brown-coloured, opaque, oblong soft gelatin capsules, measuring 15 to 19 mm in length, containing yellow viscous suspension and are imprinted in black with “NT 150”.

Each capsule contains as active substance 100 mg or 150 mg nintedanib, depending of the strength.

The excipients are:
Capsule content - medium-chain triglycerides, hard fat and polyglyceryl-3 dioleate (E475)
Capsule shell - gelatine (E441), glycerol (85%) (E422), titanium dioxide (E171), iron oxide red (E172) and iron oxide yellow (E172)
Printing ink 100 mg - shellac (E904), carmine (E 120), propylene glycol (E1520) and simeticone

Printing ink 150 mg - shellac (E904), iron oxide black (E 172) and propylene glycol (E1520).

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

The soft capsules are packed in oriented polyamide/aluminium/polyvinyl chloride-aluminium (OPA/Al/PVC-Al) unit dose perforated blisters.

II.2 Drug Substance

The drug substance is nintedanib esilate, an established substance not described in the any pharmacopoeia. The drug substance is a bright yellow, crystalline powder. Solubility in water increases at lower pH and decreases at higher pH. 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 is described in three stages as a linear five step process of four synthetic steps and a final purification/salification step. There are three starting materials declared. 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 various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided as part of the ASMF procedure. No significant changes in any parameters were observed. Based on the data submitted, a retest period could be granted of 48 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 choice of excipients is justified and their functions are explained.
The drug product was developed based on the reference product. The presented Quality Target Product Profile (QTPP) is considered appropriate in view of the intended

use of the product. Formulation and manufacturing process developments were guided by risk assessments and material attributes and process parameters with medium risks for drug product critical quality assessment were evaluated. Sufficient information has been provided on formulation and manufacturing process development.
The dissolution method is described and the discriminatory capacity of the method was demonstrated. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of gel mass preparation, content mixture preparation, encapsulation, washing and drying, printing and inspection. Process validation data on the product have been presented for three pilot scale batches for the 100 mg strength and three medium scaled batches of the 150 mg strength, in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques and the manufacturing process has been validated according to relevant European/ICH guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. and in-house requirements. These specifications 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 tests for appearance, identification, assay, related substances, uniformity of dosage units, N-nitroso desmethylnintedanib, dissolution, residual solvents and microbial quality. 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. Low 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 batches per 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 batches per strength stored at 25°C/60% RH (24 months), 30°C/75% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline, worst case conditions are used for intermediate conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. No clear trends or changes were observed in any of the tested parameters at accelerated or at long term conditions. On basis of the data submitted, a shelf life was granted of three years. The labelled storage condition is “Store in the original blister packaging 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 gelatine 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 Hexal 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)

At the time of the approval of this application, before 1 September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. At the time of approval the conclusion for this medicinal product was: since Nintedanib Hexal 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 one bioequivalence study, which is discussed below. In addition, a biowaiver of strengths is requested.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Nintedanib Hexal 150 mg, soft capsules (Hexal AG, Germany) 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 were met for the waiver for the additional 100 mg strength, according to the EMA Bioequivalence guideline:

a. the 100 mg and 150 mg strengths are manufactured by the same manufacturing process,
b. the drug input is linear over the therapeutic dose range,
c. the qualitative composition of the 100 mg and 150 mg strengths is the same,
d. 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),
e. appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline (at pH 1.2, 4.5 and 6.8). At pH 1.2 and 4.5, the calculated f_2 similarity factor could not be accurately estimated, due to a too high variability in dissolution. Applying bootstrapping showed that the lower confidence interval (CI) limit is above 50. As such, comparability has been shown. At pH 6.8, dissolution was low (<10%) for both test- and reference product. Visually comparability could be confirmed, as the difference in dissolution between both products did not exceed 10%. Moreover, bootstrapping showed that the lower CI limit is above 50. As such, comparability has been shown.

Overall, comparable dissolution has been shown between the 150 mg and the 100 mg additional strength. The waiver for additional strengths is acceptable.

Bioequivalence study BE/20/183

Design

A single-dose, open label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 48 healthy male subjects, aged 19-42 years. Each subject received a single dose (150 mg) of one of the two nintedanib formulations. The tablet was orally administered with 240 ml water after a high calorie and high fat breakfast, following an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 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 48 subjects, one subject was withdrawn in period I due to an adverse event (vomiting). The remaining 47 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=47	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	392 ± 165	421 ± 176	47 ± 21	4.50 (2.00 - 7.50)
Reference	379 ± 159	409 ± 176	49 ± 25	4.50 (2.00 - 6.00)
***Ratio (90% CI)**	1.05 (0.99 – 1.11)	--	0.99 (0.92 – 1.07)	--

$AUC_{0-\infty}$	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 t = 72 hours
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 AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nintedanib Hexal 150 mg strength is considered bioequivalent with Ofev 150 mg strength.

The results of study BE/20/183 with the 150 mg formulation can be extrapolated to the 100 mg strength, 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 Hexal. At the time of approval, the most recent version of the RMP was version 1.1 dated 15 September 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 (VTE) • Arterial thromboembolism (ATE) excluding myocardial infarction • Perforation • Hepatic failure
Missing information	• Treatment of systemic sclerosis associated interstitial lung disease (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. No new clinical studies were conducted. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Ofev 100 mg and 150 mg, soft capsules, EU/1/14/979/001-004 for the content and to the MAH house-style for the design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nintedanib Hexal 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 Hexal with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 October 2024.

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/5730/002/IA/002/G	Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking. - Changes in imprints, bossing or other markings	Yes	9-7-2025	Approved	N.A.
NL/H/5730/001-002/WS/005	Changes in the composition (excipients) of the finished product - Other excipients - Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level	Yes	29-11-2025	Approved	N.A.
NL/H/5730/001-002/WS/003	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/ biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no	Yes	8-12-2025	Approved	N.A.

	new additional data are submitted by the MAH				
NL/H/5730/001-002/WS/004	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Minor change in the manufacturing process.	No	10-12-2025	Approved	N.A.
NL/H/5730/001-002/WS/001	The update of an ASMF - including changes of the open as well as the restricted part	No	29-12-2025	Approved	N.A.
NL/H/5730/001/WS/006	Change in the batch size (including batch size ranges) of the finished product - More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms Change in coating weight of oral dosage forms or change in weight of capsule shells - Solid oral pharmaceutical forms	No	5-2-2026	Approved	N.A.