19 June 2025
EMA/212977/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nintedanib Viatris

International non-proprietary name: nintedanib

Procedure No. EMEA/H/C/006486/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
ASMF	Active Substance Master File
AUC0-t	Area under the plasma concentration vs. time curve
AUC0-∞	Area under the plasma concentration vs. time curve from time zero to infinity
AUC_%Extrap_obs	Residual area
BE	Bioequivalence
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
Cmax	Maximum plasma concentration
CV%	Coefficient of variation
DSC	Differential Scanning Calorimetry
DT_{50}	Degradation half-life of substance (in a given compartment)
EC_{50}	Effect concentration at which 50% effect (mortality, inhibition of growth, reproduction, etc) is observed compared to the control group
ECG	Electrocardiogram
ECHA	European Chemicals Agency
ERA	Environmental risk assessment
FPen	Market penetration factor
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacture practice
HBsAg	Hepatitis B Surface Antigen
HCL	Hydrochloric acid
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
ICH	International conference on harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
ILD	Interstitial lung disease
IMP	Investigational medicinal product
IPF	Idiopathic pulmonary fibrosis
IR	Infrared
K_D	Adsorption distribution coefficient
KF	Karl Fischer titration
K_{ow}	Octanol/water partition coefficient
LC/MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LDPE	Low density polyethylene
LOEC	Lowest observed effect concentration
LoQ	List of questions
MO	Major Objection
MS	Mass spectroscopy
NMR	Nuclear Magnetic Resonance
NOEC	No observed effect concentration
PAR	Public assessment report
PBT	Persistent, Bioaccumulative and Toxic (substance classification)
PDE	Permitted Daily Exposure
PEC	Predicted environmental concentration
Ph. Eur.	European Pharmacopoeia
PL	Package Leaflet
QC	Quality control
RSD	Relative standard deviation
SD	Standard deviation
SmPC	Summary of Product Characteristics
SSc-ILD	Systemic sclerosis associated interstitial lung disease
TGA	Thermo-Gravimetric Analysis
Tmax	Time of the maximum measured plasma concentration
t½	Terminal half-life

UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Viatris Limited submitted on 1 July 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Nintedanib Viatris, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 January 2024.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

- Nintedanib Viatris is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF).
- Nintedanib Viatris is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.
- Nintedanib Viatris is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs).
    - This indication has been applied for during the procedure, following approval of this indication for the reference product (Ofev)
- Nintedanib Viatris is indicated in adults, adolescents and children aged 6 years and older for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).
    - The paediatric part of this indication has been applied for during the procedure, following approval of this indication for the reference product (Ofev)

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Ofev and appropriate clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Vargatef 100 mg and 150 mg soft capsules
- Marketing authorisation holder: Boehringer Ingelheim International GmbH, Germany
- Date of authorisation: 21-11-2014
- Marketing authorisation granted by: Union
- Marketing authorisation numbers: EU/1/14/954/001-004.

Medicinal product authorised in the Union where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Ofev 100 mg and 150 mg soft capsule
- Marketing authorisation holder: Boehringer Ingelheim International GmbH, Germany

- Date of authorisation: 14-01-2015
- Marketing authorisation granted by: Union
- Marketing authorisation numbers: EU/1/14/979/001-004

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Ofev 150 mg soft capsule
- Marketing authorisation holder: Boehringer Ingelheim International GmbH, Germany
- Date of authorisation: 14-01-2015
- Marketing authorisation granted by: Union
- Marketing authorisation numbers: EU/1/14/979/003-004
- Bioavailability study number: Study 0671-18

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Jana Klimasová

The application was received by the EMA on	1 July 2024
The procedure started on	18 July 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 October 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 October 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2024

The applicant submitted the responses to the CHMP consolidated List of Questions on	21 February 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	31 March 2025
The PRAC Rapporteur's circulated the updated PRAC Assessment Report on the applicant's responses to the List of Questions to all PRAC and CHMP members on	07 April 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs' updated Joint Assessment Report on the applicant's responses to the List of Questions all CHMP members on	16 April 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 April 2025
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	19 May 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	04 June 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 June 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Nintedanib Viatris on	19 June 2025

2. Scientific discussion

2.1. Introduction

Problem statement

Interstitial lung disease (**ILD**) encompasses a large group of over 200 pulmonary disorders. While idiopathic pulmonary fibrosis (**IPF**) is the best-known progressive fibrosing ILD (as a rare progressive, fibrosing lung disease leading to decreasing lung volume and progressive pulmonary insufficiency), there is a group of patients with different underlying clinical ILD diagnoses other than IPF who develop a progressive fibrosing phenotype during the course of their disease. These ILD patients demonstrate a number of similarities to patients with IPF, with their disease being defined by the presence of progressive pulmonary fibrosis, worsening respiratory symptoms, declining lung function despite immunomodulatory therapies and, ultimately, early mortality.

Systemic sclerosis associated interstitial lung disease (**SSc-ILD**) is a disease that follows a variable and unpredictable course with diverse organ manifestations; skin sclerosis, gastrointestinal, and pulmonary involvement are often the earliest organ manifestations to appear.

This is a centralised procedure according to regulation (EC) No 726/2004 for Nintedanib Viatris, submitted by the applicant Viatris Limited as a generic of a centrally authorised medicinal product Ofev (Boehringer Ingelheim International GmbH, registered since 2015) according to Article 10(1) of Directive 2001/83/EC.

About the product

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1 3. In addition, nintedanib inhibits Lck (lymphocyte specific tyrosine protein kinase), Lyn (tyrosine protein kinase lyn), Src (proto oncogene tyrosine protein kinase src), and CSF1R (colony stimulating factor 1 receptor) kinases.

Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signalling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling in interstitial lung diseases.

In *in vitro* studies using human cells, nintedanib has been shown to inhibit processes assumed to be involved in the initiation of the fibrotic pathogenesis, the release of pro fibrotic mediators from peripheral blood monocytic cells and macrophage polarisation to alternatively activated macrophages. Nintedanib has been demonstrated to inhibit fundamental processes in organ fibrosis, proliferation and migration of fibroblasts and transformation to the active myofibroblast phenotype and secretion of extracellular matrix. In animal studies in multiple models of IPF, SSc/SSc ILD, rheumatoid arthritis associated (RA) ILD and other organ fibrosis, nintedanib has shown anti-inflammatory effects and anti-fibrotic effects in the lung, skin, heart, kidney, and liver. Nintedanib also exerted vascular activity. It reduced dermal microvascular endothelial cell apoptosis and attenuated pulmonary vascular remodelling by reducing the proliferation of vascular smooth muscle cells, the thickness of pulmonary vessel walls and percentage of occluded pulmonary vessels.

The reference medical product Ofev have been initially approved based on two double blind, randomised, placebo-controlled pivotal Phase III trials and a supportive dose-finding Phase II trial for the IPF indication, with the addition of another double-blind, randomised, placebo-controlled pivotal phase III trial for the extension in the ILD indication, and a double blind, randomised, placebo-controlled pivotal Phase III trial for the extension in the SSc indication.

Another double blind, randomised, placebo-controlled trial was carried out to extend the SSc/SSc ILD indication in children.

The applicant for Nintedanib Viatris has applied for all the indications of the reference product Ofev (nintedanib), including the paediatric extension approved on 12-February-2025. However, the paediatric formulation (25 mg soft capsule) is not available for Nintedanib Viatris.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as soft capsule contains nintedanib esilate equivalent to 100 mg or 150 mg of nintedanib as active substance.

Other ingredients are:

Capsule content: medium-chain triglycerides, lauryl macrogolglycerides, and soya lecithin (E322)

Capsule shell: gelatine, glycerol (E422), titanium dioxide (E171), iron oxide red (E172), and iron oxide yellow (E172)

Black imprint: shellac, iron oxide black (E172), ammonium hydroxide, and propylene glycol (E1520).

The product is available in aluminium/aluminium unit-dose blister packs as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of nintedanib esilate is ethanesulfonic acid-methyl (3Z)-3-{[(4-{methyl-[(4-methylpiperazin-1-yl)acetyl] amino}phenyl)amino]-(phenyl)methylidene}-2-oxo-2,3-dihydro-1H-indole-6-carboxylate (1:1) corresponding to the molecular formula $C_{31}H_{33}N_5O_4 \cdot C_2H_6O_3S$. It has a relative molecular mass of 649.76 g/mol and the following structure:

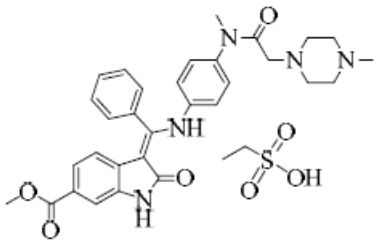

Figure 1: Active substance structure

The chemical structure of nintedanib esilate was elucidated by a combination of elemental analysis, UV analysis, FT-IR study, ^{1}H and ^{13}C NMR study, mass spectral study, DSC analysis and TGA analysis. The solid state properties of the active substance were determined by XRPD.

The active substance is a non hygroscopic pale yellow to bright greenish yellow coloured powder soluble in water, dimethyl sulphoxide and sparingly soluble in methanol. It is soluble in pH 1.2 buffer, sparingly soluble in pH 4.5 buffer and insoluble in pH 6.8 to pH 8.0 buffer solutions.

Nintedanib esilate has a non-chiral molecular structure. It contains carbon-carbon double bond which gives rise to geometrical isomerism. The manufacturing process of nintedanib esilate consistently produces Z-isomer.

Polymorphism has been observed for the active substance. The manufacturing process followed consistently produces nintedanib monoethanesulfonate hemihydrate polymorph. Polymorphic form of nintedanib esilate has been proved to be stable in micronized batches and in the long-term stability study. Thus, control of polymorphic form in the active substance specification is not considered necessary.

2.2.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by two manufacturing sites. Satisfactory GMP documentation has been provided.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Nintedanib esilate is synthesized in five main steps using five well defined starting materials with acceptable specifications.

The manufacturing process and its control has been described in sufficient detail. Reworking procedure and process of recovery of materials/solvents/reagents/intermediates/reactants/active substance have not been established.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in a clear LDPE bag which is closed and placed into LDPE black bag and closed. This double PE bag is placed inside a triple laminated bag, which is sealed and placed inside a HDPE container and sealed. The PE bags comply with EC 10/2011 as amended.

2.2.2.3. Specification(s)

The active substance specification includes tests for description (visual), solubility (Ph. Eur.), identity (IR, HPLC), ethane sulphonic acid content (potentiometry), water content (KF), sulphated ash, related substances (HPLC), assay (HPLC), residual solvents (GC), methyl ethanesulfonate, ethyl ethanesulfonate and isopropyl ethanesulfonate content (GC-MS/MS).

The proposed specification of nintedanib esilate and acceptance criteria are in line with ICH Q3A, ICH Q6A, ICH Q3C and M7.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (n=6, 5.72 kg – 19.84 kg) of the micronized and non-micronized active substance were provided. The results are within the specifications and consistent from batch to batch. No difference between micronized and non-micronized batches results can be observed.

2.2.2.4. Stability

Stability data from three production scale batches and one micronized validation batch of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25ºC/60% RH) and for up to 6 months under accelerated conditions (40ºC/75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed as part of degradation study performed for RS and assay methods on one batch. Results on stress conditions under elevated temperature, 75% RH, sunlight, water hydrolysis, acid hydrolysis, base hydrolysis and oxidation were also provided for the same batch.

The following parameters were tested*:* description, identification, water content, related substances and assay. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. Degradation products increased under accelerated conditions but remained within the specification.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months with no special storage conditions in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is presented as follows:

100 mg: peach-coloured, opaque, oblong soft-gelatine capsules, imprinted with 'JF1', and approximately 16 mm x 6 mm.

150 mg: brown-coloured, opaque, oblong soft-gelatine capsules, imprinted with 'JF2', and approximately 18 mm x 7 mm.

The finished product has been developed to be a generic equivalent to the reference medicinal product Ofev (EU/1/14/979/001-004). Consequently, the objective was to prepare a soft capsule being essentially similar to the reference medicinal product.

The active substance is soluble in water and hence there is no impact of the active substance particle size on dissolution of finished products. So it was decided to use unmicronized active substance.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. Standards except lecithin, iron oxide red, iron oxide yellow, and iron oxide black are controlled by USP/NF/EU No 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Formulation development of the finished product was initiated and finalized with similar formulation manufacturing strategy to that of the reference medicinal product formulation. The primary aim of this development was to have a formulation which is stable, robust and having comparative dissolution profile matching with the reference product. The manufacturing process involves the preparation of a suspension of the active substance in the excipients, which is then encapsulated in gelatin mass to get soft gelatin capsules.A brief manufacturing process involves medicament preparation, gelatin mass preparation, encapsulation, drying, polishing, imprinting and finally inspection

The impurity profile of the finished product has been found to be similar with the impurity profile of the reference medicinal products.

A bioequivalence study was performed on Nintedanib 150 mg soft capsules versus the respective strength of the reference product Ofev. Nintedanib 150 mg soft capsules was found to be bio-equivalent with reference product Ofev 150 mg soft capsules. In addition, comparative dissolution studies using media with three different pH were provided showing similar dissolution profiles between the test and reference biobatches.

Based on the above biowaiver of strength 100 mg has been applied and *in-vitro* dissolution data comparison of the 150 mg strength and the 100 mg strength was provided.

Initially, *in-vitro* dissolution data comparison of the batches in support of the strength biowaiver were presented. A multidisciplinary major objection (MO) was raised by the CHMP to provide comparative dissolution results between the batches. The applicant provided the comparative dissolution results. The dissolution results were evaluated, and the dissolution profiles were found to be similar. Thus, the biowaiver of the lower strength was justified.

The selection of QC dissolution method has been adequately justified. The discriminatory power of the dissolution method has been demonstrated

In relation to the manufacturing process development, the formulation and process optimization was conducted in following stages: optimization of formulation, optimization of process, and scale-up batch. Development of the finished product manufacturing process has been sufficiently described.

The primary packaging is aluminium/aluminium unit-dose blister. The material complies with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site. During evaluation a warning letter was issued for this manufacturing site by FDA the CHMP requested as MO to discuss the FDA identified findings and the impact the product applied for. The applicant responded that based on the re-evaluation of the risk's mitigation measures were evaluated and were under implementation. The CHMP requested the GMP certificate from the claimed inspection conducted for the finished product manufacturing site to verify the GMP compliance status of the site. The GMP certificate was provided, and the issue was considered solved.

The manufacturing process consists of the following steps: gelatine mass preparation, colour dispersion preparation, colour mixing process, medicament manufacturing process, encapsulation process, polishing and packaging. The process is considered to be a standard manufacturing process.

Hold time study was performed on gelatine mass, medicament, dried capsules and printed capsules. The hold times and bulk packaging are acceptable.

The manufacturing process has been sufficiently described. Critical process parameters have been presented, and the in-process controls are adequately set to control the process leading to consistent quality.

The manufacturing process has been validated on three commercial scale batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

2.2.3.3. Product specification(s)

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description (visual), average net content, identification (HPLC, UV, iron oxide, titanium dioxide), water content (KF), dissolution (UV), % LOD (Ph. Eur.), uniformity of dosage units (content uniformity), related substances (HPLC), microbial examination (Ph. Eur.), and residual solvents (GC).

The proposed finished product specification is in line with ICH Q6A and is generally acceptable for this type of dosage form. The acceptance criteria of the specification parameters are adequately justified. Limits for related substances are in compliance with the identification threshold 0.2% in line with the ICH Q3B guideline.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. Batch analysis data on two batches (one batch per strength) using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be

concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three batches of Nintedanib 100 mg and 150 mg soft capsules of commercial scale batch size confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from three commercial scale batches the finished product stored for up to 36 months under long term conditions (25ºC/60% RH) and for up to 6 months under accelerated conditions (40ºC/75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, water content, dissolution, %LOD, related substances, assay and microbial examination. The analytical methods used were the same as for release and were stability indicating.

No significant changes have been observed under long term and accelerated conditions.

Photostability study was performed in line with ICH Q1B. The finished product was found to be photo stable.

Based on available stability data, the proposed shelf-life of 3 years and without special storage conditions as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.2.3.5. Adventitious agents

Gelatine obtained from porcine sources is used in the product. Thus, no TSE CEP from suppliers of the gelatine is required.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure, two major objections were raised by the CHMP related (1) to the invitro dissolution comparative data in support of the strength biowaiver and (2) the GMP certificate of the manufacturer of the finished product. As a response, the applicant provided new comparative dissolution results, which were evaluated and were found to be similar. Thus, the biowaiver of the lower strength was justified. The applicant also provided the requested GMP certificate of the finished product manufacturing site. These responses were considered satisfactory, and the two MOs were resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Nintedanib Viatris manufactured by Viatris Limited is considered unlikely to result in any significant increase in the combined sales volumes for all nintedanib containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on the non-clinical aspects

The non-clinical sections of the SmPC are in line with the SmPC of the reference product. No additional non-clinical data has been submitted, which is acceptable, as this is a generic medicinal product. The impurity profile of Nintedanib Viatris is found to be similar with the reference product impurity profile. As no additional impurities are observed in test product, it is considered similar to the reference product.

Excipients used in this medicinal product are standard excipients used in the pharmaceutical preparations. The submitted ERA is acceptable.

2.3.4. Conclusion on the non-clinical aspects

No non-clinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for soft capsules containing nintedanib. To support the marketing authorisation application, the applicant conducted one bioequivalence study comparing Nintedanib Viatris 150 mg capsule with Ofev 150mg soft capsule with cross-over design under fed conditions. This study was the pivotal study for the application.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of nindetanib based on published literature. The SmPC is in line with the SmPC of the reference product

GCP aspect

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant submitted a bioequivalence study comparing Nintedanib Viatris 150 mg soft capsule with Ofev 150mg soft capsule. Furthermore, the applicant requested a biowaiver for the lower strength (100 mg) capsule of Nintedanib Viatris.

To support the lower strength biowaiver, the applicant met following criteria:

1) Nintedanib has linear pharmacokinetic in the proposed dose range,
2) 100 mg strength and 150 mg strength of Nintedanib Viatris are both manufactured by the same manufacturing process,
3) The qualitative composition of both strengths is the same,
4) The composition of both strengths is quantitatively proportional (gelatin capsule does not have to meet this criterion)
5) The dissolution profiles of 100 mg and 150 mg strength (biobatch) of Nintedanib Viatris are comparable at pH 1.2 and 4.5 (dissolution perfomed at 50 rmp speed using paddle apparatus). At pH 6.8, very limited dissolution is observed for both strengths.

- **Tabular overview of clinical studies**

To support the application, the applicant has submitted 1 bioequivalence study:

Table 1: Tabular overview of clinical studies

Type of study	Study Identifier	Location of Study Report	Objective(s) of the study	Study design and Type of Control	Test Product(s); Dosage Regimen; Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	0671-18	• m5-3-1-2-vol 1 of 3 • m5-3-1-2-vol 2 of 3 • m5-3-1-2-vol 3 of 3	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of nintedanib capsules 150 mg of intas pharmaceuticals ltd., india with ofev® 150 mg soft capsules of boehringer ingelheim gmbh binger strasse 173 d-55216 ingelheim am rhein, germany, in normal, healthy, adult, human male subjects under fed conditions.	Two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study, fed condition	Nintedanib capsules 150 mg, Single dose, Oral	60	Healthy, Adult, Human subjects	single dose	Complete; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 0671-18: An open label, balanced, randomized, two-treatment, two- period, two sequence, single dose, crossover, bioequivalence study of nintedanib capsules 150 mg with Ofev 150 mg soft capsules, in normal, healthy, adult, human, male subjects under fed condition

Methods

- **Study design**

Study was designed as open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover, bioequivalence study in healthy, adult, human, male subjects under fed conditions, with a screening period of 28 days prior to IMP administration in Period-I.

Study periods: Group I:

Period I: 25.12.2018 – 31.12.2018

Period II: 03.01.2019 – 09.01.2019

Group II:

Period I: 28.12.2018 – 03.01.2019

Period II: 06.01.2019 – 12.01.2019

In each study period, subjects received a single oral dose of 150 mg of nintedanib capsule (test or reference) with 240 ml of water after a high fat and high calorie vegetarian breakfast. Breakfast was served after an overnight fast of at least 10 hours and was consumed within 30 minutes. IMP was administered at 30 minutes after serving the breakfast. The capsule was swallowed whole without chewing and crushing. Wash-out period was 9 days. Blood samples were collected pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.333, 2.667, 3.00, 3.333, 3.667, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00 post-dose.

- **Test and reference products**

Product Characteristics	Test Product	Reference Product
Name	Nintedanib Capsule 150 mg	Ofev® 150 mg soft capsules (Nintedanib)
Strength	150 mg	150 mg
Dosage Form	Capsule	Capsule
Marketing Authorization Holder	-	Boehringer Ingelheim international GmbH, Bingerstrasse 173 D- 55216 Ingelheim am Rhein, Germany
Batch/Lot NUmber	PX01068	705357 (Lot No.)
Batch size (Biobatch)	40000 Capsules	-
Measured content(s)[1] (% of label claim)	99.3%	99.4%
Commercial Batch Size	-	-
Expiry date (retest date)	29 February 2020	30 April 2020
Location of Certificate of analysis	<module 5, study-reports, volume 01 to 03>	<module 5, study-reports, volume 01 to 03>
Member State where the reference product is purchased from:	-	Germany
This product was used in the following trials	0671-18	0671-18

Nintedanib Viatris 150 mg soft capsule has been compared to Ofev 150 mg soft capsules manufactured by Boehringer Ingelheim GmbH Binger Strasse 173 D-55216 Ingelheim am Rhein, Germany (Lot number 705357, exp. date of 30 April 2020).

- **Population(s) studied**

As per protocol, sixty subjects were planned for inclusion in the study.

Following inclusion criteria were applied: non-smoking, normal, healthy, adult, human volunteers between 18 and 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 and 30.0 kg/m^2 (both inclusive), were able to understand and comply with the study procedures and having given their written informed consent before they were checked in for the study. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray (posterior-anterior view) recordings.

Due to pre-dose withdrawals/discontinuations, the study was conducted on 57 subjects instead of 60 subjects. Three subjects were withdrawn post-dose. Fifty-seven subjects were analysed. Fifty-four subjects were considered for statistical analysis.

- **Analytical methods**

Bio-analytical part of the study took place in India, with samples collected during clinical study No. 0671-18. The plasma samples of subjects from the study were analysed using a validated LC-MS/MS method for nintedanib.

The bioanalytical method was validated according to in-house standards. As an internal standard, nintedanib-13CD3 was used. Calibration curves using 8-point calibration curve standards, with concentrations ranging from 0.201 ng/mL to 74.351 ng/mL, were used to determine the concentrations of nintedanib in the samples of all analysed subjects.

- **Pharmacokinetic variables**

The following pharmacokinetic parameters were calculated:

- Primary pharmacokinetic parameters:

Cmax - the maximum measured plasma concentration

AUC0-t - area under the plasma concentration vs. time curve

- Secondary pharmacokinetic parameter:

Tmax - the time of observing the peak concentration

AUC0-∞ - area under the plasma concentration vs. time curve from time zero to infinity

λ_z – terminal rate constant

t½ - terminal half-life

AUC_%Extrap_obs – the residual area

- **Statistical methods**

Descriptive statistics were computed and reported for the pharmacokinetic parameters of nintedanib. ANOVA, power and ratio analysis were computed and reported for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for nintedanib. Using two-one sided tests for bioequivalence, 90% confidence intervals for the ratio of the geometric least-squares means between drug formulations were calculated and reported for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for nintedanib.

Bioequivalence of Test Product vs. Reference Product was concluded, if the 90% confidence interval fell within the acceptance range of 80.00-125.00% for ln-transformed pharmacokinetic parameters Cmax and AUC0-t for nintedanib.

2.4.2.2. Results

Table 2: Descriptive statistics of formulation means for nintedanib (N=54)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	4.250 (1.000 - 7.000)	5.500 (1.000 - 10.017)
C_{max} (ng/mL)	57.859 ± 25.6590	56.520 ± 21.1250
AUC_{0-t} (ng.h/mL)	548.201 ± 190.4824	556.538 ± 175.3349
$AUC_{0-\infty}$ (ng.h/mL)	568.541 ± 197.0503	577.522 ± 185.0964
λ_z (1/h)	0.023 ± 0.0051	0.024 ± 0.0061
$t_{½}$ (h)	31.955 ± 7.8807	31.273 ± 9.0117
AUC_%Extrap_obs (%)	3.598 ± 1.7150	3.517 ± 1.8821

*T_{max} is represented as median (min-max) value.

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_%Extrap_obs	residual area
C_{max}	maximum plasma concentration
$T_{1/2}$	Terminal Half-life
T_{max}	time for maximum concentration (* median, range)
λ_z	Terminal rate constant

Table 3: Relative bioavailability results for nintedanib (N=54)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	53.537	53.383	100.3	94.23 - 106.74	19.5	100.0
$lnAUC_{0-t}$	517.392	529.908	97.6	94.17 - 101.23	11.2	100.0
$lnAUC_{0-\infty}$	536.862	549.514	97.7	94.27 - 101.25	11.1	100.0

- ***Safety data***

Four adverse events (AEs) were reported by 4 subjects during the conduct of the study. One AE was reported in Period-I and 3 AEs were reported in Period-II of the study. Three AEs were reported in the subjects after administration of Reference Product (headache, arthropathy, vomiting) and 1 AE was reported in the subject after administration of Test Product (headache).

All the AEs were mild in nature and all the subjects were followed up until resolution of their AEs. The causality assessment was judged as unlikely for 3 AEs and as possible for 1 AE (vomiting). There were no deaths, serious or significant AEs reported during the conduct of the study. There were no clinically significant findings in the vital signs assessment or the laboratory tests in any of the subjects.

2.4.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Discussion on clinical aspects

To support this application for marketing authorisation, the applicant submitted a review of clinical data as well as one bioequivalence study. In this application, the essential similarity is claimed to the reference medicinal product Ofev.

The bioequivalence study is an open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover, bioequivalence study in healthy, adult, human, male subjects comparing Nintedanib Viatris 150 mg capsules with Ofev 150 mg soft capsules under fed conditions. In general, the design of this study is appropriate. Statistical analysis demonstrated bioequivalence between test product and reference product.

The submitted bioequivalence study 0671-18 was performed with 150 mg strength of Nintedanib Viatris. The applicant sought to extrapolate the results of this study to 100 mg strength and requested a biowaiver for the lower strength. It is agreed that all the criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev. 1) are fulfilled, thus the lower strength biowaiver is granted for 100 mg strength.

No post-marketing data are available for Nintedanib Viatris. The medicinal product Nintedanib Viatris has not been marketed in any country.

The limited safety available with Nintedanib Viatris are in line with the known safety profile of nintedanib.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study 0671-18, Nintedanib Viatris 150 mg soft capsules is considered bioequivalent with Ofev 150 mg soft capsules.

The results of study 0671-18 with the 150 mg formulation are extrapolated to the 100 mg strength, according to the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

Therefore, the CHMP concluded that Nintedanib Viatris is bioequivalent to Ofev.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
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 teeth development disorders in paediatric population
Missing information	Treatment of SSc-ILD patients with pulmonary hypertension

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ofev. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of nintedanib soft capsules. The reference medicinal product Ofev is indicated for the treatment of idiopathic pulmonary fibrosis (IPF) in adults, for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype in adults and for the treatment of systemic sclerosis associated interstitial lung disease (ILDs) in adults, for the treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs) in children and adolescents from 6 to 17 years old and for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD) in adults, adolescents and children aged 6 years and older. Both paediatric indications were applied for during the initial marketing authorisation procedure of Nintedanib Viatris, following approval of these indications for the reference product Ofev (procedure EMEA/H/C/003821/X/0057/G, approved on 12-February-2025).

No non-clinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover design where two nintedanib 150 mg formulations (Nintedanib Viatris vs. Ofev) are administered to healthy, adult, human, male subjects under fed condition. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. A study under fed conditions is acceptable as the reference product should be taken with food, according to the SmPC. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The test formulation of Nintedanib Viatris 150 mg soft capsules met the protocol-defined criteria for bioequivalence when compared with the Ofev 150 mg soft capsules. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

The results of submitted bioequivalence study with 150 mg strength of Nintedanib Viatris can be extrapolated to the 100 mg strength, as all the criteria for granting a lower strength biowaiver are met.

Nintedanib Viatris is only available as 100 mg and 150 mg soft capsules; the paediatric formulation (25 mg soft capsule) was not applied for and is thus not available for Nintedanib Viatris. As such, the SmPC section 4.2 states that it is not possible to administer Nintedanib Viatris to paediatric patients that require less than a full 100 mg dose. If an alternative dose is required, other nintedanib products offering such an option should be used.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nintedanib Viatris is favourable in the following indications:

- Nintedanib Viatris is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF).
- Nintedanib Viatris is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.
- Nintedanib Viatris is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs).
- Nintedanib Viatris is indicated in adults, adolescents and children aged 6 years and older for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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 European Medicines Agency;
- 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.