22 February 2024
EMA/108684/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nintedanib Accord

International non-proprietary name: Nintedanib

Procedure No. EMEA/H/C/006179/0000

Note

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

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Table of contents

List of abbreviations

ASMF	Active substance master file
BCS	Biopharmaceutics classification system
CHMP	Committee for Medicinal Products for Human use
DSC	Differential scanning calorimetry
EC	European Commission
EU	European Union
FDA	Food and Drug Administration
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
LOD	Loss on drying
LDPE	Low density polyethylene
MO	Major objection
NMR	Nuclear magnetic resonance
Ph. Eur.	European Pharmacopoeia
QC	Quality control
RH	Relative humidity
SmPC	Summary of product characteristics
TGA	Thermo-gravimetric analysis
TSE	Transmissible spongiform encephalopathy
UV	Ultraviolet
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 28 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Nintedanib Accord, 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 15 September 2022.

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 is or has been granted in 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 Accord is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF).

Nintedanib Accord is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (see section 5.1).

Nintedanib Accord is indicated in adults for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

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 non-clinical and 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 number: EU/1/14/954/001-004.

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

- Product name, strength, pharmaceutical form: Ofev 100 mg and 150 mg soft capsules

- Marketing authorisation holder: Boehringer Ingelheim International GmbH, Germany
- Date of authorisation: 14-01-2015
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: 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 capsules
- Marketing authorisation holder: Boehringer Ingelheim International GmbH, Germany
- Date of authorisation: 14-01-2015
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/14/979/001-004
- Bioavailability study number(s): 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 were:

Rapporteur: Hrefna Gudmundsdottir

The application was received by the EMA on	28 November 2022
The procedure started on	28 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 March 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 April 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 April 2023
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at one finished product manufacturer located in India between 27 – 31 March 2023. The outcome of the inspection carried out was issued on 14 July 2023.	14 July 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 October 2023
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	20 November 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2023
The CHMP Rapporteur circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	7 December 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	14 December 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 January 2024
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	7 February 2024
The CHMP Rapporteur circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 February 2024
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 Accord on	22 February 2024

2. Scientific discussion

2.1. Introduction

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as soft capsules containing nintedanib esylate equivalent to 100 or 150 mg of nintedanib as active substance.

Other ingredients are:

Capsule content	Capsule shell	Printing ink
Triglycerides, medium-chain Lauroyl macrogolglycerides Lecithin (E322)	Gelatin Glycerol Titanium dioxide (E171) Iron oxide red (E172) Iron oxide yellow (E172)	Shellac Iron oxide black (E172) Ammonium hydroxide Propylene glycol (E1520)

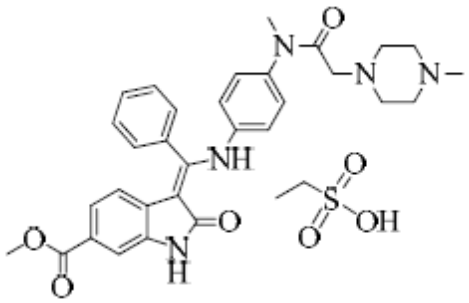
The product is available in aluminium/aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

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

Figure 1 Active substance structure



The chemical structure of nintedanib was elucidated by a combination of NMR spectroscopy, IR spectroscopy, mass spectrometry, UV spectroscopy, and elemental analysis. The solid-state properties of the active substance were measured by TGA, DSC and XRD.

The active substance is a pale yellow to bright greenish yellow coloured non-hygroscopic powder. It is soluble in neat water and at pH 1.2 but insoluble in various other pH buffers (3.0, 6.8, 7.2 and 8.0).

There is no chiral centre but nintedanib contains a tetrasubstituted olefin, as a single geometrical Z-isomer as confirmed by the structural characterisation.

Nintedanib esylate is routinely produced in the hemihydrate form as confirmed by XRD. The crystalline form was shown to be stable during storage, with no change in polymorphic form.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. The process is conducted by a single manufacturer at 2 sites.

Nintedanib is synthesised in 5 main stages of 6 chemical transformation steps using 5 well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

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. Suitable discussion and absence data has been provided for numerous potential nitrosamine impurities. None were detected and no specification limits are needed.

The active substance is packaged in a clear low-density polyethylene bag (LDPE) which is placed in LDPE black bag and closed. This double polyethylene bag is placed inside a triple laminated bag, sealed and this triple laminated bag is placed inside a HDPE container. The primary packaging material complies with EC 10/2011 as amended.

Specification

The active substance specification shown in Table 1 includes tests for description (visual), solubility (Ph. Eur.), identity (IR, HPLC), ethanesulfonic acid content (potentiometry), water content (KF), sulfated ash (Ph.

Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC), particle size (laser diffraction), microbial examination (Ph. Eur.), and sulfonate ester content (GC-MS).

Table 1 Active substance specification

Tests	Limits	Method reference
A) Microbial enumeration tests:		Ph.Eur <2.6.12> & <2.6.13>
i) Total Aerobic Microbial count:	Not more than 100 cfu/ g.	
ii) Total combined Yeasts/Moulds count:	Not more than 10 cfu/ g.	
B) Test for specified micro-organism:		
i) Escherichia coli:	Should be absent	
Methyl ethanesulfonate, Ethyl ethanesulfonate and Isopropyl ethanesulfonate content (By GC-MS)**		In-house
Methyl ethanesulfonate	Not more than 3.0 ppm	
Ethyl ethanesulfonate	Not more than 3.0 ppm	
Isopropyl ethanesulfonate	Not more than 3.0 ppm	

** To be tested one consignment every year
* Nomenclature of impurities: Related substances (By HPLC).

The specification is acceptable, limits for impurities are in line with relevant guidelines (ICH Q3A, C 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 from 3 commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 8 batches 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. 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 under long term and accelerated conditions. There was a minor increase in 1 impurity in 1 batch which nonetheless remained within specification at the end of each study.

Photostability testing following the ICH guideline Q1B demonstrated that nintedanib is not photosensitive. Forced degradation studies were performed under thermal, acidic, basic and oxidative conditions as part of analytical method validation demonstrating that the relevant analytical methods are stability indicating.

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 without special storage conditions in the proposed container.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product consists of soft gelatin capsules available in 2 strengths containing 100 or 150 mg of nintedanib as the esylate salt.

The 100 mg capsules are peach coloured, opaque, oblong shape (approximately 16 mm X 6 mm), imprinted with "JF1" in black ink containing a bright greenish yellow to pale yellow coloured suspension.

Nintedanib Accord 150 mg soft capsules

The 150 mg capsules are brown coloured, opaque, oblong shape (approximately 17.7 mm X 7 mm), imprinted with "JF2" in black ink containing a bright greenish yellow to pale yellow coloured suspension.

The capsule contents contain the same relative amounts of active substance and each excipient.

The finished product has been developed to be a generic equivalent, and thus essentially similar, to the reference medicinal product Ofev 100 mg and 150 mg soft capsules.

The physical chemical characteristics of the active substance and the reference product were studied, and the formulation developed accordingly. Nintedanib esylate has poor flow properties, is soluble in water and aqueous media below pH 4.5 and is considered BCS class II. As a result, particle size is controlled in the active substance specification.

The reference product contains medium-chain triglyceride, hard fat, soya lecithin, gelatin, glycerol (85%), titanium dioxide, iron oxide red, iron oxide yellow, shellac glaze, iron oxide black and polyethylene glycol as excipients. The applicant made several prototype formulations and compared them with the reference product in terms of dissolution characteristics, but also with a view to using the same capsule contents in each strength capsule. In the selected formulation, hard fat is replaced by lauroyl polyoxyl-6 glycerides. All excipients were shown to be compatible with the active substance and their specifications are considered appropriate. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or other pharmacopoeial standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The proposed commercial formulation is the same as that used in the bioequivalence study between reference and test 150 mg capsules which was demonstrated *in vivo*. The applicant proposed a strength biowaiver for the 100 mg capsule based on in vitro dissolution profiles. However, the originally presented data did not use the pharmacopoeial conditions as the paddle speed was too high resulting in a major objection (MO). In response, the applicant provided comparative dissolution data using a paddle speed of 50 rpm with a sinker which is considered justified. Since very little dissolution occurs at pH 6.8, data from pH 1.2 and 4.5 buffers were compared, using bootstrap f2 calculations. Based on the data provided, it is considered that the requested biowaiver of strengths is acceptable.

The QC dissolution method is based on information published by FDA's Office of Generic Drugs although different types of apparatus were tested. A sinker is needed to prevent the capsules sticking to the base of the vessel with the chosen paddle apparatus (100 rpm has been duly justified). A 0.1 M HCl was chosen as the medium since this affords sink conditions. Discriminatory power was demonstrated with respect to meaningful changes in the lauroyl polyoxyl-6 glyceride content. A MO was raised as the proposed QC limit

was considered too wide by CHMP. The applicant tightened the limit in line with applicable guidance in order to resolve this issue.

Development of the manufacturing process has been adequately described, including identification of parameters for the different stages including preparation of gelatin mass, the capsule contents and encapsulation itself.

The primary packaging is aluminium-aluminium blisters. The material complies with Ph. Eur. and 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.

Manufacture of the product and process controls

The manufacturing process along with in-process controls, consists of 5 main steps: preparation of coloured gel mass, preparation of capsule contents, encapsulation, imprinting and packaging. The process is considered to be a standard manufacturing process. The finished product is manufactured at a single site.

Major steps of the manufacturing process have been validated on 3 consecutive production scale batches. 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 and pharmaceutical form.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form including description (visual), average net content (gravimetric), identification of nintedanib (HPLC, UV), iron oxide and titanium dioxide (colorimetric), water content (capsule content, KF), dissolution (UV), loss on drying (capsule shell, (Ph. Eur.), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), microbial examination, and residual solvents.

The proposed release specifications are acceptable. The impurity profile is comparable to the reference product.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach. Based on the risk assessment, which includes test data for components of the finished product, 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 assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed 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 "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The initially provided risk assessment was considered inadequate, since it did not account for secondary amine impurities and potential degradants of the active substance potentially present in the active substance and finished product, an updated risk assessment and confirmatory testing data were requested as a MO. The applicant provided an updated risk assessment, including batch data for small molecule nitrosamines potentially present as a result of reagents and solvents used in the API process. In addition, test data of API-derived nitrosamines, including *N*-desmethyl-*N*-

nitrosonintedanib, including on expired batches, was provided. No nitrosamine impurities were detected above 10% of the respective acceptable intakes. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance, or the related finished product and no specific 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 3 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production scale batches of 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 (capsule contents), dissolution, loss on drying (capsule shells), related substances, assay, and microbial examination. The analytical methods used were the same as for release and were stability indicating. No significant trends were observed, and all parameters remained within specification throughout the studies under both sets of conditions.

The results of the photostability study conducted according to the ICH Guideline on Photostability Testing of New Drug Substances and Products show that the finished product is not sensitive to light.

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

Adventitious agents

Gelatine used in the product is obtained from porcine or avian sources, no bovine gelatine is used. Since these species are not susceptible to infection. The provided declarations are considered adequate, and no TSE are needed. No other excipients derived from animal or human origin have been used.

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. 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. Major objections were raised during the procedure relating to the demonstration of bioequivalence of the 100 mg strength, the QC dissolution method acceptance criteria, and the risk assessment for nitrosamines. All these issues were resolved in a satisfactory manner, as described in the above assessment.

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. Declarations have been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview has been provided, which is based on up-to-date and adequate scientific literature. Pharmacodynamic, pharmacokinetic and toxicological properties of nintedanib are well known. As nintedanib is a widely used, well-known active substance, the overview appropriately 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

Nintedinab Accord is a generic prescription product intended to be substituted with identical products on the marketplace. No Environmental Risk Assessment studies were submitted. However, the applicant provided calculation for the predicted environmental concentration, market penetration factor (Fpen) calculation based on the actual API consumption data and the predicted environment concentration in surface water of nintedinab. This was justified by the applicant as the introduction of Nintedanib Accord manufactured by Accord Healthcare S.L.U. 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. The CHMP agreed that no significant increase in the combined sales volumes for all nintedanib containing products and the exposure of the environment to the active substance would be expected. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The application contains an adequate review of published non-clinical data.

The pharmacodynamic, pharmacokinetic and toxicological properties of nintedanib are well known and a literature-based non-clinical overview was considered appropriate by the CHMP. The presented data for nintedanib indicates there is no risk for the environment, given the prescribed usage, and this was agreed by the CHMP.

2.3.4. Conclusion on non-clinical aspects

No nonclinical 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. There are no objections to approval of Nintedanib Accord from a non-clinical point of view.

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 with cross-over design under fed conditions. This study was the pivotal study for the application.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product. For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09 in their current version, are of particular relevance.

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

A strength based biowaiver has been applied for the additional strength 100 mg based on the in vivo data of strength 150 mg. The results of study no. 0671-18 with the 150 mg formulation can be extrapolated to the additional 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.

● Tabular overview of clinical studies

To support the application, the applicant has submitted the following study:

	An open label, balanced, randomised, two-treatment, two-sequence, two-period, single oral dose, crossover, bioequivalence study of two products of Nintedanib Capsule 150 mg in normal, healthy, adult, human, male subjects under fed condition.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

- **Study design**

The study was an open label, balanced, randomised, two-treatment, two-sequence, two-period, single oral dose, crossover, bioequivalence study of two products of Nintedanib Capsule 150 mg in normal, healthy, adult, human, male subjects under fed condition.

- **Test and reference products**

Treatment	
Treatment T (test product)	Nintedanib 150 mg, capsule, soft, Intas Pharmaceuticals Limited, India (manufacturer)
Treatment R (reference product)	Ofev® 150 mg, capsule, soft, Boehringer Ingelheim International GmbH, Germany

- **Population studied**

57 healthy Asian (non-Hispanic) male subjects (age: 31.3±5.80 years, BMI: 23.175±2.7541 kg/m^2) participated (dosed) in the study. 54 subjects completed the study and were included in the statistical and pharmacokinetic analyses of nintedanib in line with the study protocol.

- **Analytical methods**

An achiral analytical method was developed for the determination of nintedanib in human plasma and can be summarised as follows: The study samples were analysed by an LC method with MS/MS detection after solid phase extraction using nintedanib 13C-D3 as internal standard for the detection of nintedanib.

- **Pharmacokinetic Variables**

Choice of primary variables and secondary PK variables:
The parameters calculated were AUC_{0-t}, C_{max} AUC_{0-t}, T_{max}, $AUC_{0-\infty}$, AUC_%Extrap_obs, λz, and $t_{1/2}$
Primary variables: AUC_{0-t} and C_{max}
Secondary variables: T_{max}, $AUC_{0-\infty}$, AUC_%Extrap_obs, λz, and $t_{1/2}$

- **Statistical methods**

ANOVA was performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of nintedanib.
The ANOVA model included the terms Group, Sequence, Sequence*Group, Subject (Sequence*Group), Period (Group) and Formulation as fixed effects and were tested at 5% level of significance.

2.4.2.2. Pharmacokinetic conclusion

The 90% CI of the ratio for geometric least square means of ln-transformed data of C_{max} and AUC_{0-t} for nintedanib of the test product and reference product fall within 80.00%-125.00% for subjects in fed conditions indicating bioequivalence among the products.

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 pharmacology

The pivotal bioequivalence study was conducted in line with the general bioequivalence guidance in terms of design, analyte and parameters for bioequivalence assessment.

The test product was compared to the EU reference product under fed conditions in line with current guidance. The results of study no. 0671-18 indicated that the test product was bioequivalent with the EU reference product under fed conditions as the 90% CI of the ratio for geometric least square means of log-transformed data of AUC_{0-t} and C_{max} for nintedanib of the test product and reference product fell within the conventional acceptance criterion of 80.00-125.00% for subjects in fed conditions.

With regards to the extrapolation of the *in vivo* data of 150 mg to the additional strength 100 mg, similar *in vitro* dissolution among the biobatch and the additional strength has been obtained in 2 media e.g. pH 1.2 and 4.5 (as very limited dissolution is observed in pH 6.8) using conventional *in vitro* dissolution conditions. All conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6 regarding extrapolation of *in vivo* data have thus been met.

The clinical and bioanalytical site has experience with inspections. Acceptable standards of GCP of the clinical and bioanalytical sites of the submitted bioequivalence study have been assured.

2.4.4. Post marketing experience

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

2.4.5. Conclusions on clinical aspects

Based on the presented bioequivalence study Nintedanib Accord 150 mg, capsule soft is considered bioequivalent with Ofev, 150 mg, capsule, soft based on the presented study no. 0671-18.

The results of study no. 0671-18 with 150 mg formulation can be extrapolated to the additional strength 100 mg according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

Efficacy and safety of the proposed product is based on the efficacy and safety of the previously approved reference product Ofev.

2.5. Risk Management Plan

2.5.1. Safety concerns

2.5.1.1. Summary of safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
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

2.5.1.2. Discussion of the safety specification

The applicant stated that safety concerns mentioned in Module SVIII, are in line with the summary of safety concerns for the reference medicinal product Ofev, which is endorsed.

2.5.1.3. Conclusions on the safety specification

Having considered the data in the safety specification, the PRAC agrees that the safety concerns listed by the applicant are appropriate.

2.5.2. Pharmacovigilance Plan

2.5.2.1. Routine pharmacovigilance activities

The PRAC having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product. In line with the reference product, the applicant included specific adverse reaction follow-up questionnaires for:

Important identified risks

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

Important potential risks

- Arterial thromboembolism excluding myocardial infarction (note: one follow-up questionnaire for all arterial thromboembolism events)
- Perforation
- Hepatic failure

which are endorsed.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.5.2.2. Summary of additional PhV activities

Not applicable.

2.5.2.3. Overall conclusions on the PhV Plan

Having considered the data submitted, the PRAC is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.5.3. Risk minimisation measures

2.5.3.1. Routine risk minimisation measures

Routine risk minimisation activities are sufficient to manage the safety concerns of the reference medicinal product.

2.5.3.2. Summary of additional risk minimisation measures

No additional risk minimisation activities are considered warranted for this medicinal product.

2.5.3.3. Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.5.4. Summary of the risk management plan

The public summary of the RMP does not require revision.

2.5.5. Conclusion on the RMP

The PRAC considered that the risk management plan version 1.1 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

It is 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 esylate, soft capsules. The reference product Ofev is indicated as follows:

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

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical 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, randomised, two-treatment, two-sequence, two-period, single oral dose, crossover, bioequivalence study of two products of Nintedanib Capsule 150 mg in normal, healthy, adult, human, male subjects under fed condition. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. A study with subjects in fed status is acceptable as the reference product should be taken with food. 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 Accord, 150 mg, capsule, soft met the protocol-defined criteria for bioequivalence when compared with the reference product Ofev, 150 mg, capsule, soft. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

The *in vivo* data of Nintedanib Accord, 150 mg, capsule, soft can be extrapolated to the additional strength Nintedanib Accord, 150 mg, capsule, soft.

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 Accord is favourable in the following indications:

> *Nintedanib Accord is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF).*
>
> *Nintedanib Accord is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (see section 5.1).*
>
> *Nintedanib Accord is indicated in adults 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 1: Summary pf 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.