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| **February 2016** |

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| Australian Public Assessment Report for Nintedanib esilate |
| Proprietary Product Name: Ofev and Vargatef |
| Sponsor: Boehringer Ingelheim Pty Ltd |

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Common abbreviations

|  |  |
| --- | --- |
| Abbreviation | Meaning |
| Abl | Abelson wild type kinase |
| AE | Adverse Event |
| AESI | Adverse event of special interest |
| Akt | Protein kinase B |
| ALK | Anaplastic Lymphoma Kinase (also known as ALK tyrosine kinase) |
| ALT | Alanine Transaminase |
| ARTG | Australian Register of Therapeutic Goods |
| AST | Aspartate Transaminase |
| ATP | Adenosine triphosphate |
| AUC | Area under the plasma concentration time curve |
| AUC0-∞ | Area under the plasma concentration time curve from time zero to infinity |
| AUC0-24 | Area under the curve for 24 hours |
| AUC0-12 | Area under the curve for 12 hours |
| BALF | bronchoalveolar lavage fluid |
| BCRP | breast cancer resistance protein |
| BD | Twice daily |
| bFGF | basic fibroblast growth factor |
| BIBF 1202 | BIBF 1202 (the main metabolite of BIBF 1120) |
| BUN | Plasma blood urea nitrogen |
| CI | Confidence interval |
| Cmax | Maximum plasma concentration |
| CMI | Consumer Medicines Information |
| CNS | Central nervous system |
| CSR | Clinical study report |
| CT | X-Ray Computed Tomography |
| CTCAE | Common terminology criteria for adverse events |
| CV | Coefficient of variation |
| CXCL1/KC | chemokine (C-X-C motif) ligand 1/keratinocyte chemoattractant |
| CYP | Cytochrome P450 |
| CYP3A4 | CYP3A4 a member of the CYP450 family |
| DCE-MRI | Dynamic contrast-enhanced magnetic resonance imaging |
| DILI | Drug-induced liver injury |
| EC50 | Half/50% of maximal dose |
| ECG | Electrocardiograph |
| ECOG | Eastern Cooperative Oncology Group |
| EGFR | Epidermal growth factor receptor |
| EMA | European Medicines Agency |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ERAUC | Exposure ratio based on AUC |
| FDA | Food and Drug Administration |
| FGF | Fibroblast growth factor |
| FGFR | Fibroblast growth factor receptor |
| FLT3 | Fms-like tyrosine kinase-3 |
| FVC | Forced vital capacity |
| GI | Gastro intestinal |
| GIT | Gastro intestinal tract |
| GLP | Good laboratory practice |
| hERG K | Human ether-a-go-go Related Gene potassium channel |
| HNSCC | human head and neck small-cell carcinoma |
| HUASMC | human vascular smooth muscle cells |
| HUVEC | endothelial cells derived from umbilical veins |
| HR | Hazard ratio |
| HRCT | High Resolution CT scan |
| IASLC | International Association for the Study of Lung Cancer |
| IC50 | Half maximal inhibitory concentration |
| ICH | International Conference on Harmonisation |
| IL-1β | interleukin-1β |
| INR | International normalised ratio |
| IPF | Idiopathic Pulmonary Fibrosis |
| IV | Intravenous |
| Ki | Inhibitor constant |
| L | Litre(s) |
| Lck | lymphocyte specific protein tyrosine kinase |
| LFTs | Liver function tests |
| MAPK | mitogen activated protein kinase |
| MCV | Mean corpuscular volume |
| MEDRA | Medical dictionary for regulatory activities |
| MRI | Magnetic Resonance Imaging |
| MRP2 | Multi drug resistance associated protein-2 |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| NCI-H460 | National Cancer Institute – NSCLC cell line (human) |
| nRTKs | non receptor tyrosine kinases |
| NOAELs | No observable effect levels |
| NSCLC | Non-Small Cell Lung Cancer |
| OATP | organic anion-transporting polypeptide |
| OCT1 | Organic cation transporter 1 |
| OS | Overall Survival |
| PD | Pharmacodynamics |
| PDGF | Platelet derived growth factor |
| PDGFR | Platelet derived growth factor receptors |
| PFS | Progression free survival |
| P-gp | P-glycoprotein |
| PI | Product Information |
| PK | Pharmacokinetics |
| PO | Per oral |
| QoL | Quality of Life |
| QT | QT interval (in heart rate) |
| RMP | Risk management plan |
| RTKs | Receptor tyrosine kinases |
| SAE | Serious Adverse Event |
| SAFs | safety analysis sets |
| SCLC | small cell lung cancer |
| SGRQ | St George’s Respiratory Questionnaire |
| SJS | Stevens-Johnson syndrome |
| SMQ | Standardised MedDRA Queries |
| TEN | toxic epidermal necrolysis |
| TGA | Therapeutic Goods Administration |
| TGF-β2 | transforming growth factor beta 2 |
| TIMP-1 | metallopeptidase inhibitor 1 |
| TKI | Tyrosine kinase inhibitor |
| t½ | Half life |
| Tmax | The time after administration of a drug when the maximum plasma concentration is reached |
| UGT | uridine diphosphate glucuronosyltransferase |
| UIP | Usual interstitial pneumonia |
| VEGF | Vascular endothelial growth factor |
| VEGFR | Vascular endothelial growth factor receptor |
| Vss | apparent volume of distribution at steady state |
| WHO | World Health Organisation |

## I. Introduction to product submission

### Submission details

|  |  |
| --- | --- |
| *Type of submission:* | New chemical entity |
| *Decision*: | Approved |
| *Date of decision:* | 27 August 2015 |
| *Date of entry onto ARTG* | 1 September 2015 |
| *Active ingredient:* | Nintedanib esilate |
| *Product names:* | Ofev, Vargatef |
| *Sponsor’s name and address:* | Boehringer Ingelheim Pty Ltd  PO Box 1969  North Ryde NSW 2113 |
| *Dose form:* | Soft capsule |
| *Strengths:* | 100 mg and 150 mg |
| *Container:* | Blister pack |
| *Pack size:* | 60 |
| *Approved therapeutic use:* | *Ofev/Vargatef is indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after failure of first line chemotherapy*  *Ofev/Vargatef is also indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF)* |
| *Route of administration:* | Oral |
| *Dosage:* | Dosage differs for each of the indications. For details of dosage and administration please see the Product Information (PI) |
| *ARTG number (s):* | 226065, 226066, 226067, 226068 |

### Product background

This AusPAR describes the application by Boehringer Ingelheim Pty Ltd (the sponsor) to register Ofev/Vargatef for the following indications;

*Ofev/Vargatef is indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy.*

*Ofev/Vargatef is also indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF) and to slow disease progression.*

This application is for the use of nintedanib (as esilate) for two different indications, for second line use for non-small cell lung cancer (NSCLC) and for use for the treatment of idiopathic pulmonary fibrosis (IPF). The background information for each will be described separately.

Nintedanib is a tyrosine kinase inhibitor (TKI). It blocks the kinase activity of a variety of receptors:

* The vascular endothelial growth factor receptors (VEGFR) -1, -2 and -3;
* The platelet derived growth factor receptors (PDGFR) α and β;
* The fibroblast growth factor receptors (FGFR) -1, -2 and -3;

It also blocks the activity of Flt-3, Lck, Lyn and Src kinases.

##### Non-small cell lung cancer

The two major types of lung cancer are small cell lung cancer (SCLC) and NSCLC, the latter this comprises approximately 81% of lung cancers. Six percent of lung cancer originates from other cell types. The distribution of the histological types of NSCLC is: approximately 47% f adenocarcinoma histology; 25% squamous cell carcinoma; 6% large cell carcinoma and the remaining 22% are of other cell types. Some tumours have mixed histology.

About 15 to 30% of non-Asian and 30 to 60% of Asian patients with adenocarcinoma have a mutation in epidermal growth factor receptor (EGFR). Anaplastic Lymphoma Kinase (ALK) mutations are present in 2 to 7% of NSCLC patients in the US.

Treatment of advanced NSCLC aims to prolong survival and maintain quality of life, while minimising side effects of treatment. Almost all patients with advanced NSCLC eventually develop progressive disease. As well as histology, key influences on choice of initial therapy for advanced disease are:

* extent of disease (for example number and site of metastases);
* presence of symptoms related to a specific metastatic site;
* presence of driver mutations (for example EGFR; ALK; ROS proto –oncogene 1 receptor tyrosine kinase (ROS1)); and
* the patient’s overall condition and co morbidities.

Influences on choice of subsequent therapy for advanced disease are similar. Another influence is choice of prior treatment (that is the need for a non cross resistant approach).

The proposed use of nintedanib in NSCLC is based on its anti angiogenic effects mediated through inhibition of VEGF and PDGF receptors. Bevacizumab, which acts through inhibition of the VEGF pathway, has already been registered for use in NSCLC.

##### Idiopathic pulmonary fibrosis

IPF is a specific form of chronic, progressive interstitial pneumonia of unknown cause. It generally occurs in older adults, is limited to the lungs and is associated with a histological/radiological appearance known as ‘usual interstitial pneumonia (UIP)’. It is a rare condition with a prevalence estimated at between 2 and 29 cases per 100,000 of the population. IPF is a fatal condition with a median survival of 2 to 3 years after diagnosis.

The mechanism of action for the IPF indication is by inhibition of PDGFR, and possibly of VEGFR. In response to alveolar epithelial cell injury, PDGF stimulates proliferation, migration and survival of fibroblasts, which in turn produce extracellular matrix proteins. In fibrotic diseases, fibroblasts exhibit unregulated proliferation, differentiate into myofibroblasts, and deposit excessive connective tissue products in the alveolar wall, creating fibrotic foci. The aetiology of the initial cell injury is unknown.

There are currently no drugs registered in Australia that have been proven to be of benefit in the treatment of IPF. Drugs that have been used include corticosteroids, immunosuppressive agents, colchicine, acetylcysteine, interferon gamma 1b, bosentan and etanercept. A new agent, pirfenidone, has in recent years been approved for the treatment of IPF in several foreign markets (including the USA, Europe and Canada). However, at the time of writing of this review it had not been registered in Australia.

Preclinical data suggest a potential role of fibroblast growth factor (FGF) and platelet derived growth factor (PDGF) signalling in the pathogenesis of IPF. Hence, the clinical rationale is based on the ability to nintedanib inhibit the receptors for these factors.

The recommended dose of nintedanib for the treatment of IPF is 150 mg twice daily administered approximately 12 hours apart, and for the treatment of NSCLC is 200 mg twice daily administered approximately 12 hours apart, on Days 2 to 21 of a standard 21 day docetaxel treatment cycle. The PI states that nintedanib must not be taken on the same day of docetaxel chemotherapy administration (Day 1).

### Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 1 September 2015.

At the time the TGA considered this application, a similar application had been approved or was under consideration in the countries/jurisdictions as is shown in Table 1.

Table 1. Overseas regulatory status.

|  |  |  |
| --- | --- | --- |
| Country | Submission Date | Status |
| **NSCLC indication** | | |
| European Union (Centralised Procedure) | 30 September 2013 | Approved |
| United States of America | Not submitted |  |
| Canada | 28 March 2014 | Ongoing |
| New Zealand | 26 September 2014 | Ongoing |
| Singapore | 26 January 2015 | Ongoing (priority review) |
| Switzerland | 20 December 2013 | Withdrawn |
| **Idiopathic Pulmonary Fibrosis (IPF) indication** | | |
| European Union (Centralised Procedure) | 5 May 2014 | Approved 15 January 2015 |
| United States of America | 2 May 2014 | Approved 15 October 2014 |
| Canada | 26 June 2014 | Approved 25 June 2015 |
| New Zealand | 26 September 2014 | Ongoing |
| Singapore | 26 January 2015 | Ongoing (priority review) |
| Switzerland | 12 June 2014 | Approved 13 August 2015. |

### Product information

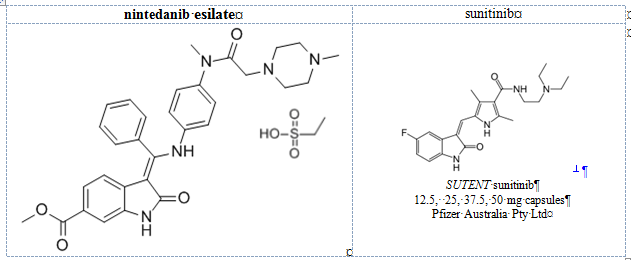
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Quality findings

### Introduction (if applicable)

Boehringer Ingelheim Pty Ltd has applied to register Ofev and Vargatef soft capsules containing 100 mg and 150 mg nintedanib (formulated with 120.4 or 180.6 mg of nintedanib esilate). The active is a new chemical entity with the structure below. It is an antineoplastic agent belonging to the class of tyrosine kinase inhibitors. It is structurally related to other inhibitors in this class such as sunitinib. Figure 1 compares the chemical structure of nintedanib esilate and sunitinib.

Figure 1. Structure of nintedanib esilate and sunitinib.



The capsules are proposed for use, in combination with docetaxel, in the treatment of patients with locally advanced, metastatic or recurrent NSCLC of adenocarcinoma tumour histology after first line chemotherapy and for the treatment of IPF and to slow disease progression.

The recommended maximum dose is 400 mg (given 200 mg, two capsules, twice daily). The capsules should be taken with food, swallowed whole with water and should not be chewed or crushed. As a new drug, nintedanib esilate is not the subject of a pharmacopoeial monograph.

### Drug substance (active ingredient)

Nintedanib is a bright yellow crystalline powder. It contains no chiral centres but the double bond at C‑3 of the indole moiety allows for E/Z isomerism. It is manufactured as the Z‑isomer. There is only one known polymorph.

The solubility of nintedanib esilate is strongly pH dependent with an increased solubility in acid (pH < 3). The solubility decreases by at least three orders of magnitude between pH 3 and pH 6. Thus there is a possibility of reduced bioavailability in achlorhydric patients.

Levels of impurities in the drug substance are low (below the accepted threshold for identification, 0.10%). Residual solvents used in the synthesis of the drug are also adequately controlled. Particle size has been identified as a critical parameter and is also appropriately controlled in the drug substance. The drug substance exhibits good stability and the data provided supports a retest period of 60 months.

### Drug product

The drug product is an immediate release, soft gelatin capsule containing 100 mg or 150 mg of nintedanib (as esilate) as a bright yellow viscous suspension. The 100 mg capsules are peach coloured, opaque and oblong shaped (approximately 6.2 x 16.3 mm). The 150 mg soft capsules are brown coloured, opaque and oblong shaped (approximately 7.1 x 17.6 mm). Both strengths are printed with the Boehringer Ingelheim company symbol and the capsule strength.

Figure 2. Image of dosage form of both strengths of Ofev/Vargatef.



The capsule fill comprises of nintedanib esilate suspended in a mixture of hard fat, triglyceride and lecithin. The 100 and 150 mg capsules have the same qualitative composition of the fill mix.

The drug substance is only very slightly soluble in the fill mix. The particle size is a critical attribute to avoid agglomerates in the fill mix and therefore is controlled. There was no evidence of drug substance particle size changes in the capsules when stored under long term and accelerated conditions. The fill mix is injected into semi formed soft gelatin capsules and the capsule halves are sealed.

The drug product specification includes control for degradation products in accord with TGA adopted guidelines.

Capsules are packed in Aluminium (Al)/Al blisters (packs of 60). Stability data generated under long term, intermediate and accelerated conditions support a shelf life of 36 months when stored below 25°C.

The drug product aspects are acceptable.

### Biopharmaceutics

Nintedanib esilate is classified as a drug substance with low solubility according to the Biopharmaceutics Classification System. It does not have straightforward pharmacokinetic and metabolic properties during the absorption phase and cannot be classified as either high permeability or low permeability.

The following bioavailability and bioequivalence data were submitted:

#### Trial No: 1199.75

Trial No: 1199.75 showed that the absolute bioavailability of 100 mg nintedanib administered as a soft capsule under fed conditions in health subjects relative to a 6 mg intravenous (IV) dose administered as a 4 hour infusion based on area under the plasma concentration time curve from time zero to infinity (AUC0-∞)was 4.7% (90% confidence interval (CI) 3.6 to 6.1). Low bioavailability was attributed to either extensive first pass metabolism and/or a low absorption due to P-glycoprotein (P-gp) mediated efflux in the gut.

#### Trial No: 1199.17

Trial No: 1199.17 assessed the effect of food on single oral doses of 150 mg nintedanib (3 x 50 mg capsules) after a high fat, high calorie breakfast relative to administration after an overnight fast. The 50 mg capsules contained the same fill mix as the proposed capsules and only differ by dose strength and capsule colour. When administered under fed conditions, the absorption of nintedanib was delayed (median time after administration of a drug when the maximum plasma concentration is reached (Tmax); fasted: 2.00 hours; fed: 3.98 hours). Maximum plasma concentration (Cmax) and AUC0-∞ increased by about 20% when nintedanib was administered with food (Cmax fasted and fed were 11.1 ng/mL and 13.2 ng/mL, respectively; AUC0-∞ fasted and fed were 98.4 ng.h/mL and 110 ng.h/mL, respectively). The inter subject variability of total exposure, area under the plasma concentration time curve (AUC) also increased under fed conditions (AUC0-∞ %g CV fasted 33% and fed 53.9%).

#### Trial No: 1199.21

Trial No: 1199.21 assessed the relative bioavailability of fast and slowly dissolving 50 mg capsules and a 1 mg/mL oral solution under fed conditions. Bioequivalence was established between the fast dissolution and slow dissolution 50 mg capsules. The oral solution is not intended for marketing.

The composition of the capsule fill was unchanged during Phase I to III development. Only the colour of the capsule shell, the printing and the size of the capsules were changed. Comparative dissolution data was provided to show that these changes are not expected to affect bioavailability. As the same fill is used for both capsule strengths, a study of the bioequivalence of the 100 mg and 150 mg capsules is not needed.

### Quality summary and conclusions

Registration is recommended in respect of chemistry, manufacturing and controls and biopharmaceutics aspects.

## III. Nonclinical findings

### Introduction

The submitted nonclinical dossier was in accordance with the relevant International Conference on Harmonisation (ICH) guidelines. The overall quality of the dossier was high with all pivotal safety studies conducted under good laboratory practice (GLP) conditions.

### Pharmacology

#### Primary pharmacology

##### Mechanisms of action

Nintedanib is a small molecule that inhibits several receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). RTKs inhibited by nintedanib include platelet derived growth factor receptor (PDGFR) α and β (half maximal inhibitory concentration (IC50) approximately 60 nM), FGFR 1-3 (IC50 37 to 108 nM), and VEGFR 1-3 (IC50 13 to 34 nM). It is also a potent inhibitor of Fms-like tyrosine kinase-3 (FLT3) (IC50 26 nM), lymphocyte specific protein tyrosine kinase (Lck) (IC50 16 nM) and Abelson wild type kinase (Abl) (IC50 41 nM), and a moderate inhibitor of Lyn (IC50 195 nM) and Src (IC50 156 nM). Inhibition of FLT3 might be the cause of effects on the haematopoietic system observed in repeat dose toxicity studies (see discussion below). Some toxicity findings might be explained by the inhibition of Lck, Lyn and Src, which are members of the Src family kinases and play important roles in cellular signal transduction in multiple systems.[[1]](#footnote-2),[[2]](#footnote-3)

Receptors for angiogenic/pro fibrotic growth factors such as the members of the VEGFR, FGFR and PDGFR families are essential regulators of tumour angiogenesis and of fibroblast proliferation and migration. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation, migration and transformation of fibroblasts, as well as the proliferation and survival of endothelial as well as perivascular cells (pericytes and vascular smooth muscle cells) in tumour tissues.

###### Pharmacodynamic effects - IPF

IPF is a chronic, progressive fibrosing interstitial pneumonia of unknown cause, associated with the histopathological and/or radiologic pattern of usual interstitial pneumonia. It is a fatal disease, with median survival time of 2 to 3 years following diagnosis. The mechanism of action for the IPF indication is by inhibition of PDGFR, and possibly of VEGFR. In response to alveolar epithelial cell injury, PDGF stimulates proliferation, migration and survival of fibroblasts, which in turn produce extracellular matrix proteins. In fibrotic diseases, fibroblasts exhibit unregulated proliferation, differentiate into myofibroblasts, and deposit excessive connective tissue products in the alveolar wall, creating fibrotic foci. The aetiology of the initial cell injury is unknown. Experimental evidence in rats suggests that inhibition of VEGF receptors may reduce fibrosis.[[3]](#footnote-4)

In vitro studies showed that nintedanib inhibited proliferation and PDGFR auto phosphorylation in human lung fibroblasts from IPF patients or normal subjects, with half/50% of maximal dose (EC50) values in the nanomolar range (< 100 nM). The EC50 values in the inhibition of PDGF-, FGF- and VEGF-stimulated human lung fibroblasts proliferation were 11, 5.5 and less than 1 nM, respectively. At higher concentrations (> 100 nM), it also inhibited transforming growth factor beta-2 (TGF-β2)-induced fibroblast to myofibroblast transformation and migration in primary human fibroblasts from IPF patients.

Three animal models of pulmonary fibrosis (bleomycin induced lung fibrosis in mice and rats and silica induced lung fibrosis in mice) were used to assess the in vivo efficacy of nintedanib to inhibit lung fibrosis and inflammation. In the rat model, preventive treatment from the first day of lung fibrosis induction nearly completely inhibited fibrotic changes of the lung at 41.5 mg/kg/day, demonstrated by near normal lung histology and complete inhibition of fibrosis related marker genes TGF-β1 and procollagen I. Treatment after the onset of fibrotic changes (Day 10 after induction of lung fibrosis with bleomycin) also resulted in a nearly complete attenuation of fibrosis as assessed histologically and by gene expression. Preventative treatment at lower doses showed variable responses at 24.9 mg/kg/day and no effects at 8.3 mg/kg/day. Plasma drug concentrations were not measured in the study. Based on the toxicokinetic data on Day 14 in the 2 week repeat dose toxicity study (U06-1063), the Cmax and area under the curve for 24 hours (AUC0-24) of nintedanib at 41.5 mg/kg/day was approximately 40 ng/mL and 380 ng∙h/mL, similar to the respective values (32 ng/mL and 363 ng∙h/mL) in IPF patients at the proposed clinical dose (150 mg twice daily (BD)).

In the bleomycin induced lung fibrosis mouse model, preventive (Day 0 to Day 14 of bleomycin administration) dosing of ≥ 24.9 mg/kg/day nintedanib, as well as therapeutic (Day 7 to Day 21 of bleomycin administration) dosing of 49.8 mg/kg/day nintedanib, significantly decreased inflammation (reduced lymphocyte counts in the bronchoalveolar lavage fluid (BALF) and interleukin-1β (IL-1β) in lung tissue) and fibrosis (reduced TIMP-1 – a metalloproteinase inhibitor, total lung collagen levels in lung tissue, and histological changes).

In the silica induced mouse model of mixed lung inflammation and fibrosis, preventive (Days 0 to 30 of silica administration) dosing of nintedanib at ≥ 24.9 mg/kg/day reduced inflammation and fibrosis by chemical analysis and histological examination. Reduced inflammation markers were neutrophils and lymphocytes (not on macrophage counts) in BALF, and IL-1β, chemokine (C-X-C motif) ligand 1/keratinocyte chemoattractant (CXCL1/KC), TIMP-1 and total collagen in lung homogenate. Histologically, lung inflammation, granuloma and fibrosis were alleviated in nintedanib treated animals. Therapeutic (Days 10 to 30 of silica administration) dosing of nintedanib at the same doses reduced neutrophils and lymphocytes in the BALF, total lung collagen and the fibrotic score in a comparable manner to the preventive treatment. However, compared to the preventive treatment, the reduction of IL-1β, CXCL1/KC, TIMP-1, inflammatory score and granuloma score was smaller. When treatment was administered from Day 20 to Day 30, only the lymphocyte count in BALF was significantly reduced, suggesting that the timing after the initial injury and/or treatment duration correlate with efficacy.

In summary, nintedanib is effective in reducing pulmonary fibrosis and inflammation in animal models of pulmonary fibrosis. Response to nintedanib treatment may be dependent on timing after the initial injury[[4]](#footnote-5), [[5]](#footnote-6) and/or treatment duration.

###### Pharmacodynamic effects - NSCLC

Angiogenesis is a crucial step for malignant tumour growth and metastasis. Vascular endothelial growth factor (VEGF), via VEGFRs on endothelial cells, stimulates normal and disease associated angiogenesis. The PDGF and FGF pathways are also believed to play important roles in tumour growth. PDGF receptors are important for signalling in perivascular smooth muscle cells and pericytes and FGF receptors are believed to provide an escape mechanism with tumour cells switching from VEGF to FGF signalling to attract endothelial cells.

Treatment of VEGF stimulated endothelial cells derived from umbilical veins (HUVEC) and skin micro vessels (HSMEC) with nintedanib resulted in inhibition of cell proliferation and apoptosis (EC50 9 to 12 nM) and inhibition of the phosphorylation of cell survival signalling molecules, mitogen activated protein kinase (MAPK) and protein kinase B (Akt) at > 100 nM. Inhibition of basic fibroblast growth factor (bFGF) stimulated HUVEC proliferation required higher drug concentrations (EC50 approximately 300 nM), associated with suppression of the activation of both MAPK and Akt at > 100 nmol/L. The apoptosis marker, cleaved caspase-3 was up regulated in a concentration dependent manner in both VEGF and bFGF stimulated HUVEC. Similar activities were observed in human vascular smooth muscle cells (HUASMC) stimulated by PDGF-BB (IC50 43 to 69 nM for cell proliferation; inhibition of MAPK and Akt, and activation of caspase 3 at > 100 nmol/L).

In pericyte assays, nintedanib inhibited proliferation of PDGF-BB stimulated (bovine retinal) pericytes (IC50 79 nM), and activation of MAPK at 100 nM. As for HUVEC and HUASMC, activation of Akt in pericytes was also suppressed by nintedanib after stimulation with PDGF-BB or bFGF. However in contrast to endothelial and smooth muscle cells, inhibition of this pathway in pericytes did not increase cleaved caspase-3 (apoptosis marker).

In vitro studies in VEGFR-2 transfected NIH3T3 cells showed a sustained inhibition of VEGFR-2 related processes. Exposure to nintedanib (50 nM for 1 hour) inhibited VEGFR phosphorylation up to 32 hours after the removal of nintedanib. Sustained inhibition was also seen in HUVEC cells; nintedanib (50 nM for 2 hours) still resulted in inhibition of proliferation (by 96 to 98%) after a 22 to 46 hour drug free period.

Nintedanib (at > 3.5 µM) did not inhibit the proliferation of cancer cells (human epithelial cancer cell lines FaDu, Calu-6, and HeLa), which do not express VEGFR, FGFR or PDGFR, consistent with its mechanisms of action.

Anti-tumour efficacy was studied in nude mouse models implanted with human NSCLC cells. In Calu-6 NSCLC xenografts, nintedanib (50 mg/kg/day orally (PO) for 20 or 36 days) inhibited tumour growth by 64 to 76%. A greater anti-tumour effect was observed with the nintedanib/pemetrexed combination (83% inhibition; pemetrexed alone inhibited tumour growth by 51%). In National Cancer Institute NSCLC cell line (NCI-H460) NSCLC xenografts, nintedanib (25 mg/kg/day PO for 30 days) inhibited tumour growth by 46%, with synergistic or additive effects in combination with docetaxel (7.5 mg/kg IV once weekly; no inhibition by docetaxel alone and 70% inhibition by the combination) and vinorelbine (5 mg/kg IV once weekly; 20% inhibition by vinorelbine alone and 76% inhibition by the combination). No additional adverse effects were observed in animals treated with either combination.

Efficacy against tumour growth was also demonstrated in mouse models of FaDu human head and neck small-cell carcinoma (HNSCC), Caki-1 human renal carcinoma, GS-9L glioblastoma (rat model), HT-29 colorectal cancer, SKOV-3 ovarian cancer and PAC-120 prostate carcinoma, with tumour growth inhibition ranging from 64% to 89% at 50 or 100 mg/kg/day PO. The decrease in tumour growth was associated with deceased vessel density in the Caki-1 xenografts (by approximately 80% at 100 mg/kg/day). Minimal or no effects were seen at lower doses (< 25 mg/kg/day). The Cmax and AUC0-24 in mice after a single PO dose of 100 mg/kg nintedanib were 327 ng/mL and 2263 ng∙h/mL, respectively, and the respective values in rats at 50 mg/kg/day PO were 93.5 ng/mL, AUC0-24 473 ng∙h/mL, compared with the mean clinical values of 43.2 ng/mL and 540 ng∙h/mL in NSCLC patients.

In all tumour models tested, nintedanib is active at tolerated doses (50 to 100 mg/kg daily PO) in the inhibition of tumour growth. The nonclinical in vitro and in vivo studies support the clinical indication.

###### Pharmacological activity of BIBF 1202 (main human metabolite of nintedanib)

The pharmacological activity of BIBF 1202 (the main metabolite of BIBF 1120) was studied in VEGFR-2, VEGFR-3, FGFR1 and PDGFRα kinase assays, VEGF- and bFGF-stimulated HUVEC proliferation, PDGFR α and β autophosphorylation assays and in a murine model of FaDu human HNSCC tumour. The metabolite was generally less potent than nintedanib (see Table 2).

Table 2. Potency comparison of nintedanib and BIBF 1202.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Nintedanib | BIBF 1202 | Relative potency of metabolite *cf.* parent drug (%) |
| Inhibition of VEGFR-2 (IC50: nM) | 21 | 62 | 33.9 |
| Inhibition of VEGFR-3 (IC50: nM) | 13 | 14.5 | 89.7 |
| Inhibition of FGFR1 (IC50: nM) | 69 | 240 | 28.8 |
| Inhibition of PDGFRα (IC50: nM) | 59 | 433 | 13.6 |
| Inhibition of autophosphorylation of PDGFRα (EC50: nM) | 21.6 | 5717 | 0.4 |
| Inhibition of autophosphorylation of PDGFRβ (EC50: nM) | 38.7 | 23510 | 0.2 |
| Inhibition of VEGF stimulated HUVEC proliferation (EC50: nM) | approximately 10 | 80 | 12.5 |
| Inhibition of bFGF dependent HUVEC proliferation (EC50: nM) | 290 | 3400 | 8.5 |
| *In vivo* anti-tumour efficacy at 30 mg/kg IP, HNSCC murine xenograft model (T/C: %) | 8 | 64 | \* |

\* The parent drug inhibited tumour growth by 92% (compared to control), while the metabolite (even at 5 times the parent drug plasma levels) only inhibited tumour growth by 36% (compared to control).

Although BIBF 1202 is a potent inhibitor of the VEGFR-2 and VEGFR-3 kinases, it shows low activity in the auto-phosphorylation of PDGFR and VEGF and FGF stimulated HUVEC proliferation and no significant anti-tumour efficacy (at least in the FaDu tumour model) despite higher drug plasma levels than the parent drug.

There were no pharmacology studies on BIBF 1202 glucuronide, which is also a major human metabolite. Given the high plasma concentration of BIBF 1202 glucuronide in humans (steady state AUC approximately 10 fold higher than the AUC of nintedanib) the absence of pharmacology studies on this metabolite is considered a major deficiency.

##### Secondary pharmacodynamics and safety pharmacology

Radioligand receptor assays were used to determine the affinity of nintedanib for various receptors. Out of 50 receptors tested, nintedanib at 5 µM inhibited adenosine A3 receptors by 66% and adenosine A2A receptors by 56%, NK2 receptors by 84%, 5HT1B receptors by 102% (but < 25% inhibition in another assay), muscarinic M2 receptors by 54%, histamine H2 receptors by 51% and L-type calcium channels by 65%. No clinically relevant effects are expected on these receptors tested due to the fact that these percentages of inhibition for receptor binding was determined at a concentration (5 µM) > 2,000 fold higher than the unbound clinical Cmax (2.4 nM nM for NSCLC and 1.8 nM for IPF).

Specialised safety pharmacology studies assessed effects on the cardiovascular, respiratory and central nervous systems. Additional studies on renal and gastrointestinal effects were performed. Only one of the studies (CNS study) was GLP compliant. Most of these experiments used the chloride salt (BIBF 1120 CL).

###### Effect on cardiovascular function

Inhibition of Human ether-a-go-go Related Gene potassium channel (hERG K) + current was seen in vitro (IC50 4 µM; > 1500 times the unbound clinical Cmax). In isolated guinea pig papillary muscles, concentrations up to 10 µM nintedanib did not affect the action potential.

In anaesthetised domestic pigs (experiments not feasible in dogs due to the induction of diarrhoea), increasing doses (3, 10 and 30 mg/kg) of nintedanib by IV infusion, at 30 minute intervals, caused reversible small decreases in systolic and diastolic blood pressures (< 10%) and approximately 30% decreases in maximal left ventricular dP/dt, after starting the infusion of the highest dose. No significant changes were observed in heart rate or electrocardiograph (ECG). However, increased systolic arterial blood pressure (by approximately 10 mm Hg) was observed in rats after a PO dose of 100 mg/kg nintedanib (Cmax 3 to 5 times the clinical value, based on the rat pharmacokinetic data in Study U02-1381).

In a 4 week oral toxicity study (GLP compliant) in Cynomolgus monkeys, there was no effect on systolic or diastolic blood pressure or ECG parameters (measured at 2 and 24 hours after treatment on Day 1 and Week 4), except for a minor increase (5.7%) in heart rate in the high dose group (60 mg/kg/day) 2 hours after dosing on Day 1. The mean Cmax at 60 mg/kg/day was approximately 275 ng/mL, 3 to 5 times the clinical Cmax.

Nintedanib is not expected to have significant adverse effects on cardiovascular functions in patients.

###### Effect on respiratory function

In two whole body plethysmography studies in conscious rats, a single oral dose of ≤ 100 mg/kg nintedanib did not affect respiratory rate, tidal volume or minute volume.

###### CNS effects

No effects on general behaviour and locomotor activity were seen in mice and rats at an oral dose up to 300 mg/kg and 100 mg/kg, respectively. No signs indicative of CNS effects were observed in single dose (up to 2,000 mg/kg in mice and rats) and repeat dose toxicity studies (in several animal species). Tissue distribution studies in rats showed negligible distribution of nintedanib related materials to the brain.

###### Effect on renal function

Nintedanib caused a slight decrease in urine glucose excretion, and increases in urine volume, urine sodium, calcium and beta-N-acetylglucosaminidase in rats at 100 mg/kg/day PO after the first dose. The effects on urine volume, sodium and calcium were reversible by Day 6 despite continued dosing. Plasma blood urea nitrogen (BUN) and creatinine levels were unaffected. There was no consistent renal toxicity in repeat dose toxicity studies.

###### Gastrointestinal effects

In rats, a single oral dose of nintedanib at > 30 mg/kg caused dose dependent inhibition of gastro intestinal tract (GIT) movement, with gastric emptying reduced by 50% to 230% (measured by gastric content weight, significant only at 100 mg/kg) and intestinal transit decreased by 28% to 40% (no effect at 10 mg/kg). Gastric secretion was unaffected in rats at an intra-duodenal dose of up to 100 mg/kg. The GIT movement may be slowed in IPF and NSCLC patients taking nintedanib.

###### Safety pharmacology of metabolite BIBF 1202

No safety pharmacology studies were performed with the major metabolite BIBF 1202. Human pharmacokinetic data demonstrated that human plasma levels of BIBF 1202 and its glucuronide, comprise up to 32% and 47% of total reactivity following a 100 mg nintedanib dose. Although BIBF 1202 have demonstrated in vitro effects similar to nintedanib, its potency was significantly lower, and there was no significant pharmacodynamic activity in vivo in a mouse tumour model. Nonclinical pharmacokinetic and toxicokinetic data showed the exposure to BIBF 1202 following oral dosing of nintedanib, with high levels detected in rats.

In summary, effects on cardiovascular, renal, respiratory and CNS functions in patients are not predicted by animal studies. Gastrointestinal effects (reduced GIT movement, in addition to other effects observed in repeat dose toxicity studies, see below) are predicted by nonclinical studies.

### Pharmacokinetics

Absorption from the intestinal tract following oral (PO) administration is incomplete (since biliary excretion is higher following IV administration than PO administration), therefore limiting oral bioavailability. There were no sex differences in exposure in nonclinical species.

The oral bioavailability was low in rats (approximately 11%), rhesus monkeys (23.8%) and humans (4.7%). Intestinal P-gp activity and first pass metabolism in the intestine and liver (by ester cleavage) contribute to the low bioavailability of nintedanib.

The prevalent metabolic reaction (about 25% ester cleavage compared to about 5% Cytochrome P450 (CYP) dependent metabolism in human hepatic microsomes in vitro) was the hydrolysis/cleavage of nintedanib by esterases to the carboxylate metabolite, BIBF 1202. BIBF 1202 is subsequently glucuronidated by uridine diphosphate glucuronosyltransferase (UGT) enzymes (hepatic UGT 1A1 and intestinal UGT 1A7, UGT 1A8, and UGT 1A10) to BIBF 1202 glucuronide. The circulating metabolites BIBF 1202 and especially BIBF 1202 glucuronide were mainly formed pre-systemically after oral dosing of nintedanib. Metabolism of nintedanib by CYP450 was only a minor part of its biotransformation, with CYP3A4 being the predominant enzyme in the oxidation of nintedanib. There were some indications for a minor contribution of CYP2C8 to the oxidative metabolism of nintedanib.

Hydrolysis of nintedanib to the carboxylate metabolite, BIBF 1202, and subsequent conjugation to BIBF 2012 glucuronide is the major metabolic pathway in humans and animal species despite quantitative differences between species. In humans, the steady state plasma AUCs of BIBF 1202 and its glucuronide were approximately 1.5 and 10 times the AUC of nintedanib. In comparison, steady state exposures (based on AUC) to the metabolites (relative to the parent compound) were low in mice (BIBF 1202: 10% to 30%; BIBF 1202 glucuronide: similar to parent compound) and rhesus monkeys (BIBF 1202: < 10%; BIBF 1202 glucuronide: similar to parent compound after a single dose (not measured in repeat dose toxicity studies)) and high in rats (BIBF 1202: 2 to 4 times the parent; BIBF 1202 glucuronide: > 40 times the parent). While M7 (glucuronide of nintedanib) accounting for 9% to 12% of total drug related material in human plasma was not detected in plasma of animal species, a small amount of the oral dose was recovered in rhesus and human urine (0.02% to 0.03% of dose) after an oral dose of nintedanib, suggesting that this metabolite was formed in monkeys. Thus the animal models used in toxicity studies for nintedanib are appropriate. Exposures to nintedanib and its main metabolites in animal species are compared with the human exposure in Tables 2 to 4.

Plasma protein binding was high in rhesus and Cynomolgus monkeys (7% to 9% unbound fraction) and even higher in in mice, rats and humans (2.5% to 3% unbound fraction). Albumin was the major binding protein in human plasma. Low to moderate binding was observed for the metabolite, BIBF 1202 (unbound fraction: approximately 33% in Rhesus plasma and 32% to 33% in rat and human plasma) and high binding for BIBF 1202 glucuronide (unbound fraction: 16% in Rhesus plasma and 3% to 4% in rat and human plasma). Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.87 in human blood.

Following IV dosing tissue levels were well above blood levels as early as 5 minutes after dosing, and the volume of distribution was greater than total body volume (apparent volume of distribution at steady state (Vss) 41.2, 8.6 to 10.4 and 13.6 L/kg in rat, monkey and human, respectively), suggesting extensive extravascular distribution. Consistent with this tissue distribution in rats was rapid and wide following oral dosing with radio labelled nintedanib. Aside from organs involved in excretion, high levels of radioactivity were seen in the testes, salivary gland, epididymis and liver, after repeated oral dosing. There was negligible distribution into the CNS.

The distribution of radioactivity in pigmented rats resembled that found in albino rats, but radioactivity in the eye was more pronounced in pigmented rats 2 hours after dosing and was still clearly visible at 168 hours post dose, indicating a specific affinity to the melanin containing layer in the eye. However, pigmented skin did not show elevated radioactivity compared to non pigmented skin and the concentration in skin was similar to blood levels.

Excretion of nintedanib and/or its metabolites (radioactivity following oral dosing with radio labelled nintedanib) was primarily via the bile and faeces. Excreted material from nonclinical species consisted predominantly of metabolites, while the parent drug comprised 10% to 30% of the radioactivity in the faeces (12% to 14% in mice, 16% in rats, 34% in Rhesus monkeys and 20% in humans).

High radioactivity levels were detected in the stomach and intestines after IV administration, indicating gastro intestinal (GI) and biliary secretion of nintedanib and/or metabolites. Faecal excretion accounted for more than 90% of the dose, while the contribution of renal excretion to the total clearance was low (< 5%). The clearance of nintedanib was faster in nonclinical species (30, 37 and 202 mL/min/kg in rhesus monkeys, Cynomolgus monkeys and rats, respectively) than in humans (18 mL/min/kg), with shorter elimination half-life (t½) in animals (4 to 7 hours) than in humans (12 to 18 hours).

##### Pharmacokinetic drug interactions

###### Interactions via CYP450 and UGT

Oxidation by CYP450 is only a minor pathway of nintedanib metabolism. Nintedanib was not an inhibitor (or caused only weak inhibition) of CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 and 4A11, although assays for 2C8, 2C19 and 4A11 were not validated using a positive control inhibitor. Nintedanib inhibited erythromycin N-demethylation (by CYP3A4) with an IC50 of 70.1 µM, but caused no or only weak inhibition of nifedipine oxidation (no inhibition), midazolam hydroxylation (36% at 100 µM) or testosterone 6β-hydroxylation (all catalysed by 3A4). No significant inhibition of any above CYP450 was observed for the metabolites, BIBF 1202 and BIBF 1202 glucuronide. In vitro (human hepatocytes) and in vivo (rat) studies showed no significant induction of CYP450 (CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A4, 2E and 4A). CYP450 inducers or inhibitors are unlikely to affect the disposition of nintedanib, and nintedanib is not expected to alter the pharmacokinetics of CYP450 substrates.

The glucuronidation of BIBF 1202 is catalysed by UGT1A1, 1A7, 1A8 and 1A10. Nintedanib was shown to be a competitive inhibitor of this enzyme (inhibitor constant (Ki) 12.6 µM) using BIBF 1202 as the substrate. Another assay with oestradiol as the substrate gave an IC50 value of 24.5 µM against the formation of estradiol-3-glucuronide by the same enzyme. Nintedanib also inhibited UGT2B7 (IC50 77.6 µM). The Ki and IC50 values against UGT1A1 and UGT2B7 are more than 150 times the clinical Cmax (80 nM for the NSCLC indication, not accounting for protein binding). BIBF 1202 was not an inhibitor of either enzyme. There were no studies investigating the potential activity of BIBF 1202 glucuronide on UGT. Given the high plasma concentration of this metabolite in patients (around 10 times the concentration of nintedanib), it is recommended that the activity of BIBF 1202 on UGT be investigated as a post approval requirement if nintedanib may be used with drugs predominantly metabolised by glucuronidation.

###### Interactions via transporters

The transport of nintedanib and its two main metabolites, BIBF 1202 and BIBF 1202 glucuronide by P-gp, multi drug resistance associated protein-2 (MRP2) and breast cancer resistance protein (BCRP) were studied in cells expressing these efflux transporters. The studies showed that nintedanib is a substrate of P-gp, and BIBF 1202 glucuronide is a substrate of MRP2 and BCRP. Increased intestinal absorption was demonstrated in isolated intestinal loops of rats in situ in the presence of zosuquidar, a P‑gp inhibitor. The nonclinical findings indicate interactions with P-gp inhibitors and inducers in humans. This was confirmed by clinical studies with rifampicin (a P-gp inducer) and ketoconazole (a P-gp inhibitor). The elimination of BIBF 1202 glucuronide may be altered by MRP2 and BCRP inhibitors or inducers.

In vitro assays using uptake transporter expressing cells showed rapid cellular uptake of nintedanib due to strong binding of the drug to cell surface and/or rapid diffusion into cells; transporters tested were organic anion-transporting polypeptide (OATP); OATP1B1, OATP1B3, OATP2B1, Organic cation transporter (OCT); OCT1 and OCT2. The mechanisms of cellular uptake of nintedanib were not reliably identified, although the assays suggest nintedanib is unlikely to be a substrate of the transporters except for OCT1, which was shown to transport nintedanib into cells faster than negative control cells (not expressing OCT1).

The metabolite BIBF 1202 was shown to be a substrate of OATP1B1 and OATP2B1, but not a substrate of OATP1B3, OCT1 or OCT2 and nor was the metabolite BIBF 1202 glucuronide a substrate of OATP1B1, OATP1B3, OATP2B1 or OCT1. The involvement of other transporters (for example bile salt export pump (BSEP), OAT) in the distribution/excretion of nintedanib and its major metabolites was not studied.

Nintedanib was shown to have low potential for the inhibition of BCRP (50% to 60% inhibition at 3 to 30 µM, not dose dependent) and P-gp (around 30% inhibition at 0.3 to 3 µM, but no inhibition at 30 µM). It did not significantly inhibit OATP1B1, OATP1B3, OATP2B1, OCT2 or MRP2 activities. Nintedanib caused a dose dependent inhibition of OCT1 (IC50 0.88 µM), and weak inhibition of BCRP (50% to 60% inhibition at 3 to 30 µM, not dose dependent) and P-gp (around 30% inhibition at 0.3 to 3 µM, but no inhibition at 30 µM). These findings are considered to be of low clinical relevance since human Cmax (60 to 80 nM, unbound concentration 1.8 to 2.4 nM) is considerably lower than the inhibitory concentrations.

The metabolite BIBF 1202 did not inhibit P-gp, MRP2 or OCT2, and showed only weak inhibition of BCRP (20% to 30% inhibition at 3 to 30 µM). BIBF 1202 showed dose dependent inhibition of OATP1B1 (IC50 14 µM), OATP1B3 (IC50 79 µM), OATP2B1 (IC50 50 µM) and OCT1 (IC50 16 µM). These findings are of low clinical relevance since the IC50 values were more than 500 fold higher than the clinical unbound Cmax for this metabolite (9.2 to 12.4 ng/mL or 17.6 to 23.6 nM).

The metabolite BIBF 1202 glucuronide was shown not to be an inhibitor of P-gp, BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3 and OCT2 at concentrations up to 100 µM.

### Toxicology

##### Acute toxicity

The maximum non-lethal dose of BIBF 1120 was ≥ 2,000 mg/kg in both mice and rats. At the maximum feasible IV dose in mice and rats (due to maximum concentration and volume) of 40 mg/kg, no evidence of acute toxicity was observed. These studies in rats and mice indicated a low acute toxic potential of nintedanib by the clinical route.

##### Repeat-dose toxicity

GLP compliant repeat dose toxicity studies of up to 3 months in mice, 6 months in rats and 52 weeks in monkeys were conducted. Non GLP studies of up to 1 week duration in minipigs and one 2 week GLP study in dogs were also submitted. The duration of the pivotal studies, group sizes and the use of both sexes were consistent with International conference on harmonisation (ICH) guidelines.[[6]](#footnote-7), [[7]](#footnote-8). The dog was ruled out as a relevant species for repeat dose toxicity testing, because severe gastrointestinal effects would have prevented this species from attaining sufficient long term exposure. The same occurred with minipigs.

The choice of species in the pivotal studies (rat as the rodent and monkeys as the non-rodent species) is acceptable based on pharmacodynamic/pharmacokinetic considerations. Dosing was by the intended clinical route (PO) in all pivotal studies (some IV studies were also submitted). The dosage regimen in the animal studies does not fully replicate the clinical situation. Dosing in all studies was only once daily, whereas dosing clinically is intended to be twice daily. Although this is a deficiency, in vitro pharmacological studies indicated sustained activity on VEGFR over a 32 hour period. The highest doses used resulted in reduced body weight gain or body weight loss in rodents and monkeys, and gastrointestinal disturbances (vomiting and diarrhoea) in monkeys, suggesting the maximum tolerated dose was achieved.

###### Relative exposure

Relative (animal/human) exposures to the parent drug (based on AUC) achieved at the highest doses were 3 to 5 in rats and 6 to 9 in monkeys (Table 3). Relative exposures for nintedanib at the no observable effect levels (NOAELs) were consistently ≤ 2. Animal to human exposure comparisons (average of males and females in all species) shown in the tables below are based on the total rather than the free fraction of the parent drug and metabolite BIBF 1202 glucuronide, since no significant differences in free fraction were observed. Exposure ratios for metabolite BIBF 1202 are based on its free fraction due to significantly lower protein binding in rhesus monkeys than in humans (unbound fraction 45% in monkey plasma compared with 22% in human plasma).

While there was no data on the pharmacological activity of BIFB 12020 glucuronide, the other main human metabolite, BIBF 1202 is pharmacologically active with similar potency against VEGFR kinases despite lower activity against FGFR and PDGFR than the parent compound and lack of in vivo efficacy in a murine xenograft tumour model. The exposures of animal species to the metabolites are also compared with human exposure in separate tables below. Adequate exposures to the human metabolites (BIBF 1202 and the glucuronide conjugate) were achieved in the rat (13 to 52 weeks) studies (higher animal/human exposure ratios than the ratios for the parent drug) but exposures to BIBF 1202 in monkeys were very low (exposure ratios < 0.5, compared to exposure ratios up to 4 for the parent drug in the 52 week study). The plasma concentration of BIBF 1202 glucuronide was not measured in repeat dose toxicity studies in monkeys. Based on plasma concentrations after a single dose of nintedanib in rhesus monkeys (concentrations similar to the parent drug), monkeys were exposed to this metabolite in the repeat dose studies, probably at similar levels to the parent drug. However, the animal/human exposure ratio for monkeys would be low because of very high levels of BIBF 1202 glucuronide in human plasma.

For risk assessment, the most weight should be placed on the exposure ratios based on the parent drug, since in vivo and in vitro pharmacological activity for the main metabolite, BIBF 1202 was shown to be generally less than the parent drug (except for similar affinity for VEGFR), and the majority of the toxicity findings can be attributed to pharmacological action (see below). In the toxicity discussion below, the animal/human exposure ratios (ER) are based on nintedanib AUC for NSCLC patients. The exposure ratio based on AUC (ERAUC) for IPF patients are 1.5 fold higher than for NSCLC patients.

Table 3. Exposures to nintedanib in oral repeat dose toxicity and carcinogenicity studies.

| Species | Study duration time of measurement | Dose mg/kg/day | Cmax ng/mL | AUC0–24 h ng∙h/mL | Exposure ratio# IPF indication | | Exposure ratio# NSCLC indication | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Based on Cmax | Based on AUC | Based on Cmax | Based on AUC |
| **Mouse** | 13 weeks (Day 87) | 10 | 56.95 | 228 | 1.8 | 0.63 | 1.3 | 0.42 |
| 30 | 251.5 | 1315 | 7.9 | 3.6 | 5.8 | 2.4 |
| 100 | 1025 | 4735 | 32 | 13 | 24 | 8.8 |
| Carcinogenicity (week 26) | 5 | 18.75 | 40.15 | 0.59 | 0.11 | 0.43 | 0.07 |
| 15 | 82.2 | 340.5 | 2.6 | 0.94 | 1.9 | 0.63 |
| 30 | 261.5 | 1335 | 8.2 | 3.7 | 6.1 | 2.5 |
| **Rat** | 4 weeks (Day 28) | 3 | 7.02 | 10.53 | 0.2 | 0.03 | 0.2 | 0.02 |
| **20** | 52.25 | 134 | 1.6 | 0.4 | 1.2 | 0.3 |
| 100 | 313 | 1545 | 9.8 | 4.3 | 7.3 | 2.9 |
| 13 weeks (week 13) | **3** | 2.14 | 5.35 | 0.1 | 0.01 | 0.1 | 0.01 |
| 20 | 62.6 | 216.5 | 2.0 | 0.6 | 1.5 | 0.4 |
| 100 | 246.5 | 1640 | 7.7 | 4.5 | 5.7 | 3.0 |
| 13 weeks (Day 87) | 5 | 5.32 | 24.4 | 0.2 | 0.1 | 0.1 | 0.1 |
| 20 | 31 | 179 | 1.0 | 0.5 | 0.7 | 0.3 |
| 60 | 39.65 | 374 | 1.2 | 1.0 | 0.9 | 0.7 |
| 26 weeks (Day 164-179) | **5** | 7.41 | 22.8 | 0.2 | 0.1 | 0.2 | 0.04 |
| 20 | 59.75 | 250 | 1.9 | 0.7 | 1.4 | 0.5 |
| 80 | 170.5 | 1135 | 5.3 | 3.1 | 4.0 | 2.1 |
| Carcino­genicity (week 52) | 2.5 | 0.8935 | 1.66 | 0.03 | 0.005 | 0.02 | 0.003 |
| 5 | 4.935 | 25.85 | 0.15 | 0.07 | 0.11 | 0.05 |
| 10 | 9.83 | 82.95 | 0.31 | 0.23 | 0.23 | 0.15 |
| **Monkey (rhesus)** | 4 weeks (Day 27) | **10** | 63.3 | 443 | 2.0 | 1.2 | 1.5 | 0.8 |
| 20 | 136 | 1057.5 | 4.3 | 2.9 | 3.2 | 2.0 |
| 60 | 253.5 | 3225 | 7.9 | 8.9 | 5.9 | 6.0 |
| 52 weeks (Day 363) | 10 | 65.65 | 646 | 2.1 | 1.8 | 1.5 | 1.2 |
| 20 | 112 | 1025.5 | 3.5 | 2.8 | 2.6 | 1.9 |
| ≥ 30 | 126 | 1380 | 3.9 | 3.8 | 2.9 | 2.6 |
| **Monkey (Cynomolgus)** | 4 weeks (Day 28) | **3** | 16.9 | 171.5 | 0.5 | 0.5 | 0.4 | 0.3 |
| 15 | 114.3 | 1315 | 3.6 | 3.6 | 2.7 | 2.4 |
| 60 | 272 | 2619 | 8.5 | 7.2 | 6.3 | 4.9 |
| 13 weeks (Day 91) | 3 | 37.75 | 325 | 1.2 | 0.9 | 0.9 | 0.6 |
| 15 | 135.5 | 1340 | 4.2 | 3.7 | 3.1 | 2.5 |
| 30/20 | 144.5 | 1595 | 4.5 | 4.4 | 3.3 | 3.0 |
| **Human** | IPFa | 150 mg BID | 31.95 | 363 | 1 | 1 | NA | NA |
| NSCLCa | 200 mg BID | 43.2 | 540 | NA | NA | 1 | 1 |

# = animal: human Cmax and AUC0-24; a = AUC and Cmax was calculated using the clinical dose of 150 mg BID (IPF) and 200 mg BID (NSCLC) and estimated AUC and Cmax values obtained from the Summary of Clinical Pharmacology Studies, where AUC0-12 was 1.21 ng∙h/mL/mg and Cmax was 0.213 ng/mL/mg in IPF patients and AUC0-12 was 1.35 ng∙h/mL/mg and Cmax was 0.263 ng/mL/mg in NSCLC patients; bold and underlined dose was NOAEL; NA = not applicable.

Table 4. Exposures to BIBF 1202 in oral repeat dose toxicity and carcinogenicity studies.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Study duration and time of measure-ment | Dose mg/kg/day | Cmax ng/mL | AUC 0‑24 hng∙h/mL | Exposure ratio# IPF indication | | Exposure ratio# NSCLC indication | |
| Based on Cmax | Based on AUC | Based on Cmax | Based on AUC |
| Mouse | 13 weeks Day 87 | 10 | 10.5 | 40.9 | 0.25 | 0.07 | 0.19 | 0.05 |
| 30 | 54 | 310 | 1.3 | 0.57 | 0.96 | 0.38 |
| 100 | 374.5 | 1405 | 8.9 | 2.6 | 6.6 | 1.7 |
| Carcinogenicity week 26 | 5 | 3.6 | 5.5 | 0.09 | 0.01 | 0.06 | 0.01 |
| 15 | 33.2 | 111.4 | 0.79 | 0.20 | 0.59 | 0.14 |
| 30 | 71.2 | 394.5 | 1.7 | 0.72 | 1.3 | 0.49 |
| Rat | 13 weeks Day 87 | 5 | 16 | 86.95 | 0.38 | 0.16 | 0.28 | 0.11 |
| 20 | 59.3 | 454.5 | 1.4 | 0.83 | 1.1 | 0.56 |
| 60 | 104.8 | 1000 | 2.5 | 1.8 | 1.9 | 1.2 |
| 26 weeks Day 164-179 | 5 | 12.2 | 55.9 | 0.29 | 0.10 | 0.22 | 0.07 |
| 20 | 121.1 | 553.5 | 2.9 | 1.0 | 2.2 | 0.68 |
| 80 | 527 | 2490 | 12.6 | 4.6 | 9.3 | 3.1 |
| Carcino­genicity week 52 | 2.5 | 4.29 | 15.5 | 0.10 | 0.03 | 0.08 | 0.02 |
| 5 | 14.7 | 105.8 | 0.35 | 0.19 | 0.26 | 0.13 |
| 10 | 34.9 | 243 | 0.83 | 0.45 | 0.62 | 0.30 |
| Monkey rhesus | 52 weeks Day 363 | 10 | 4.8 | 66.8 | 0.23 | 0.25 | 0.17 | 0.17 |
| 20 | 6.0 | 75.2 | 0.29 | 0.28 | 0.22 | 0.19 |
| ≥ 30 | 7.2 | 93.5 | 0.35 | 0.35 | 0.26 | 0.24 |
| Human | IPFa | 150 mg BID | 42 | 546 | 1 | 1 | NA | NA |
| NSCLCa | 200 mg BID | 56.4 | 812 | NA | NA | 1 | 1 |

# = animal: human Cmax and AUC0-24 normalised to unbound fraction (22% in rat and human plasma, 45% in monkey plasma); a = AUC and Cmax was calculated using the clinical dose of 150 mg BID (IPF) and 200 mg BID (NSCLC) and estimated AUC and Cmax values obtained from the Summary of Clinical Pharmacology Studies, where AUC0-12 was 1.82 ng∙h/mL/mg and Cmax was 0.280 ng/mL/mg in IPF patients and AUC0-12 was 2.03 ng∙h/mL/mg and Cmax was 0.282 ng/mL/mg in NSCLC patients; bold and underlined dose was NOAEL; NA = not applicable.

Table 5. Exposures to BIBF 1202 glucuronide in oral repeat dose toxicity and carcinogenicity studies.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species | Study duration time of measurement | Dose mg/kg/day | Cmax ng/mL | AUC0–24 h ng∙h/mL | Exposure ratio# IPF indication | | Exposure ratio# NSCLC indication | |
| Based on Cmax | Based on AUC | Based on Cmax | Based on AUC |
| Mouse | 13 weeks (Day 87) | 10 | 63.3 | 197.5 | 0.28 | 0.04 | 0.21 | 0.03 |
| 30 | 228.5 | 968.5 | 1.0 | 0.22 | 0.75 | 0.16 |
| 100 | 1011 | 5050 | 4.4 | 1.2 | 3.3 | 0.86 |
| Carcino­genicity (week 26) | 5 | 16.5 | 42.7 | 0.07 | 0.01 | 0.05 | 0.01 |
| 15 | 78.6 | 399.5 | 0.34 | 0.09 | 0.26 | 0.07 |
| 30 | 213.5 | 1291 | 0.94 | 0.29 | 0.70 | 0.22 |
| Rat | 13 weeks (Day 87) | 5 | 780.5 | 2065 | 3.4 | 0.47 | 2.6 | 0.35 |
| 20 | 2425 | 8150 | 11 | 1.9 | 8.0 | 1.4 |
| 60 | 6865 | 30000 | 30 | 6.8 | 23 | 5.1 |
| 26 weeks (Day 164-179) | 5 | ND | ND | - | - | - | - |
| 20 | ND | ND | - | - | - | - |
| 80 | ND | ND | - | - | - | - |
| Carcinogenicity (week 52) | 2.5 | 295.5 | 1149 | 1.3 | 0.26 | 0.97 | 0.20 |
| 5 | 667 | 2985 | 2.9 | 0.68 | 2.2 | 0.51 |
| 10 | 1245 | 5565 | 5.5 | 1.3 | 4.1 | 0.95 |
| Monkey (rhesus) | 52 weeks (Day 363) | 10 | ND | ND | - | - | - | - |
| 20 | ND | ND | - | - | - | - |
| ≥ 30 | ND | ND | - | - | - | - |
| Human | IPFa | 150 mg BID | 228 | 4410 | 1 | 1 | NA | NA |
| NSCLCa | 200 mg BID | 304 | 5880 | NA | NA | 1 | 1 |

# = animal: human Cmax and AUC0-24; a = AUC and Cmax was calculated using the clinical dose of 150 mg BID (IPF) and 200 mg BID (NSCLC) and estimated AUC and Cmax values obtained from the Summary of Clinical Pharmacology Studies, where AUC0-12 was 14.7 ng∙h/mL/mg and Cmax was 1.52 ng/mL/mg in IPF patients and AUC0-12 was 14.7 ng∙h/mL/mg and Cmax was 1.52 ng/mL/mg in NSCLC patients; bold and underlined dose was NOAEL; ND = no data; NA = not applicable.

##### Major toxicities

Major toxicity findings included reduced red blood cells and effects on bone, bone marrow, gastrointestinal tract, liver, kidney, female reproductive organs and lymphoid tissues, all of which are associated with or secondary to the pharmacological activity of nintedanib.

The chronic 6 month rat study identified a NOAEL of 5 mg/kg/day (ERAUC < 0.1). In the chronic 12 month monkey study, no NOAEL was identified, but the only finding at the lowest dose, 10 mg/kg/day (ERAUC 1.2) was thickening of femur growth plate, which is not clinically relevant for adult patients.

###### Bone marrow, haematopoiesis and coagulation

Although tyrosine kinase inhibitors have been known to induce thrombocytopenia, no significant reductions in platelet counts were observed in animal species dosed with nintedanib. Platelets were only decreased in one study in mice (100 mg/kg/day for 13 weeks; ERAUC 9) and one study in rhesus monkeys (≥ 30 mg/kg/day for 52 weeks; ERAUC 2.6), whereas platelets were increased in rats (ERAUC up to 3) receiving nintedanib for 13 to 26 weeks (3 studies) and Cynomolgus monkeys receiving nintedanib for 4 weeks (ERAUC 5). Coagulation was slightly accelerated in the rat carcinogenicity study (10 mg/kg/day; ERAUC 0.15) and in male rhesus monkeys receiving 60 mg/kg/day for 4 weeks (ERAUC 6). Based on the nonclinical findings, there is no significant increase of bleeding risk in patients receiving nintedanib.

Cellular depletion of the bone marrow was observed in mice (100 mg/kg/day for 13 weeks; ERAUC 9), rats (≥ 20 mg/kg/day for 26 weeks; ERAUC 0.5), rhesus monkeys (20 mg/kg/day for 2 weeks) and Cynomolgus monkeys (≥ 3 mg/kg/day for 13 weeks; ERAUC 0.6). Interestingly, rats receiving 100 mg/kg/day for 2 weeks displayed hyperplasia of the bone marrow. Circulating lymphocytes were slightly increased in rodents and decreased in monkeys (further discussed below). White blood cell counts were only increased in the 26 week repeat dose study in rats (ERAUC ≥ 0.5) and in one of the non-pivotal IV studies in Cynomolgus monkeys.

Decreases in red blood cells were observed in rats at ERAUC ≥ 0.3, in mice at ERAUC ≥ 2.4, in rhesus monkeys at ERAUC > 2, and in Cynomolgus monkeys at ERAUC 5. Associated with anaemia were splenic extramedullary haematopoiesis in rats at 80 mg/kg/day for 26 weeks (ERAUC 2), and hepatic extramedullary haematopoiesis in rats receiving ≥ 20 mg/kg/day for 26 weeks (ERAUC ≥ 0.5) and in male mice at 100 mg/kg/day for 13 weeks (ERAUC 9). The effects on bone marrow and red blood cell counts in animal studies suggest that anaemia may occur in patients treated with nintedanib.

###### Lymphopoietic system

In oral studies in rats, decreased weight and apoptosis of the thymus were observed at exposures lower than those expected in patients (at 20 mg/kg/day for 13 weeks and 100 mg/kg/day for 4 weeks), and thymus involution was observed at ERAUC > 2 (80 mg/kg/day for 26 weeks, and 100 mg/kg/day for 13 weeks). Similar effects were observed in Cynomolgus monkeys, including decreased weight and apoptosis of the thymus (≥ 20 mg/kg/day for 13 weeks; ERAUC) ≥ 3) and thymus cellular depletion (60 mg/kg/day for 4 weeks; ERAUC 5), and in 2 week IV studies in rhesus monkeys.

In rats, mild effects were observed in the lymph nodes, such as apoptosis (100 mg/kg/day for 4 weeks; ERAUC 3), decreased organ weights (100 mg/kg/day for 13 weeks; ERAUC 3), and decreased cellularity (60 mg/kg for 13 weeks; ERAUC 0.7).

Nintedanib induced effects in the spleen were observed in rats and monkeys. In rats, splenic apoptosis was observed in animals receiving 100 mg/kg/day for 4 weeks (ERAUC 3) and splenic lymphoid depletion in animals receiving 100 mg/kg/day for 13 weeks (ERAUC 3) and 80 mg/kg/day for 26 weeks (ERAUC 2). Cynomolgus monkeys receiving 60 mg/kg/day for 4 weeks (ERAUC 5) displayed splenic lymphoid depletion accompanied by decreased relative spleen weight (compared with body weight).

Nintedanib inhibits tyrosine kinases such as Lck, Lyn and Src (members of the Src family kinases), but no consistent adverse effects on lymphocyte subpopulations in blood, spleen and thymus, as well as spleen natural killer cell activity of rats treated for 4 weeks, Cynomolgus monkeys treated for 13 weeks and Rhesus monkeys treated for 52 weeks. There were no consistent changes in blood lymphocyte counts; small increases or decreases of lymphocytes were observed in different species. Although the haematological changes do not suggest increased infections, liquid faeces, associated with the presence of mixed coliform Spp. and/or Campylobacter Spp., was observed in the 52 week study in rhesus monkeys. Due to the pharmacological activities of nintedanib and lymphoid depletion observed in animal studies, opportunistic infections in patients cannot be ruled out as a potential adverse effect.

###### Bone

The bone was a target organ in all animal species studied. Oral administration of nintedanib caused thickening of the growth/epiphyseal plate in mice (≥ 30 mg/kg/day), rats (≥ 5 mg/kg/day), dogs (≥ 10 mg/kg/day) and rhesus monkeys (≥ 10 mg/kg/day) with exposures slightly higher than the clinical exposure (ERAUC 1 to 4). These effects were reversed in the rats (4 week recovery after 13 week treatment) and partially reversed in the rhesus monkey (8 week recovery after 52 week treatment). Thickening of the growth plate was accompanied in rodents by (non-reversible) articular cartilage chondrocyte swelling. Similar bone effects have been reported in rodent studies with other VEGFR inhibitors. VEGF has been shown to be involved in cartilage remodelling, ossification and angiogenesis during endochondrial bone formation.[[8]](#footnote-9) Therefore, these effects on bones were probably due to the pharmacological activity of the drug. Rhesus monkeys were affected as well, but these monkeys were < 3 years of age (not adults yet). As primate physes have minimal to no postpubertal growth (unlike the physes of rodents), these bone effects are expected to have minimal relevance to adult patients with closed physes.

###### Renal effects

Renal mesangial hypertrophy (also described as thickening of the mesangium) and cytoplasmic inclusion bodies were observed in rats receiving ≥ 100 mg/kg/day PO for 2 weeks. Thickening of the mesangium was also seen in rats receiving nintedanib 20 mg/kg/day IV. In rats receiving 80 mg/kg/day nintedanib for 26 weeks (ERAUC 2), several renal effects were observed, including periodic acid-Schiff stain (PAS) positive hyaline droplets, basophilic tubules, mononuclear infiltration, tubular protein casts, increased fat droplets in the tubular epithelium, and increased deposits of tubular pigment. The presence of hyaline droplets (not completely reversible) and glomerulopathy was also observed in rats receiving 100 mg/kg/day for 13 weeks (ERAUC 3). In the rat carcinogenicity study, the incidence and severity of chronic progressive nephropathy were increased at ≥ 5 mg/kg/day (below clinical exposure).

Tubular dilatation was observed in Cynomolgus monkeys receiving 60 mg/kg/day for 4 weeks (ERAUC 5) although this finding was not observed in studies of longer duration.

In the kidney, VEGF expression is prominent in glomerular podocytes and in tubular epithelial cells, and VEGF receptors are found on preglomerular, glomerular, and peritubular endothelial cells. VEGF is required for growth and proliferation of glomerular and peritubular endothelial cells.[[9]](#footnote-10) Although different kidney injuries have been observed after treatment with VEGF inhibitors,[[10]](#footnote-11) since renal parameters of clinical chemistry did not accompany the histopathological effects in the rats (suggesting normal renal function), and renal effects were not consistently seen in the monkeys, the risk of renal toxicity in patients is low.

###### Hepatotoxicity

Liver haemosiderosis accompanied by increased relative liver weight (compared with body weight) was observed in rats which received ≥ 20 mg/kg/day for 26 weeks (ERAUC 2; reversible after 8 weeks) as well as rats which received 100 mg/kg/day for 13 weeks (ERAUC 3; almost completely reversible after 4 weeks). Increases in alanine transaminase (ALT) and aspartate transaminase (AST) were observed in several repeat dose oral studies in rats at ERAUC ≥ 1. They were both increased in an IV study in the rat as well. Increased ALT and AST were also observed in Cynomolgus monkeys (at ERAUC 5) and in rhesus monkeys (at ERAUC 6), without haemosiderosis. Hepatic toxicity is a risk in patients.

###### Gastrointestinal disturbances

Liquid faeces, reduced food consumption and thin appearance were observed at doses as low as 3 mg/kg in dogs. One dog receiving 10 mg/kg and all receiving ≥ 30 mg/kg had to be euthanised before the end of treatment due to adverse gastrointestinal effects (liquid faeces, vomiting, salivation) and paralysis/abnormal motor activity. Severe GI toxicity was also seen in mini pigs. In studies using ≥ 40 mg/kg/day nintedanib, five of six mini pigs had to be euthanised due to severe gastrointestinal signs (emesis, soft or liquid faeces), and abnormal gait. Despite the severity of the GIT clinical signs, only inconsistent or moderate increases in liver transaminase activities were observed in dogs and mini pigs. The severity of the GIT signs would have made it difficult to obtain significant exposures in these species. Therefore, dogs and mini pigs were ruled out as appropriate animal models for nintedanib.

Slightly increased incidences of thickening of the duodenum were observed in rats in 13 week (60 mg/kg/day, ERAUC 1) and 26 week (80 mg/kg/day, ERAUC 2) studies. Vomiting or diarrhoea were not observed in rodents. In a 4 week study in Cynomolgus monkeys, ≥ 15 mg/kg/day nintedanib (ERAUC 2.4) induced diarrhoea, soft and coloured faeces and vomiting. Monkeys receiving 60 mg/kg/day (ERAUC 5) had to be euthanised due to severe diarrhoea, vomiting, reduced food consumption and body weight as well as poor general health condition. In rhesus monkeys, administration of ≥ 20 mg/kg/day nintedanib ( ERAUC ≥ 2) for 4 weeks induced coloured faeces, and doses ≥ 30 mg/kg/day (ERAUC ≥ 2.6) for 52 weeks induced liquid faeces, vomiting, pale gums, salivation, low bodyweight gain and the presence of mixed coliform Spp. and/or Campylobacter Spp in faecal and rectal swabs. Exposure (AUC) at the NOEL for gastrointestinal findings in monkeys was 2 times the clinical exposure. Overall, the studies indicate that gastrointestinal disturbances (vomiting and diarrhoea) may be seen in patients taking nintedanib.

###### Ovaries

Ovarian changes were limited to rodents. Decreased number of mature corpora lutea and increased number of luteinised follicles were observed in mice at 100 mg/kg/day for 13 weeks (ERAUC 9), and increased number of luteinised follicles and small corpora lutea were seen in rats at 100 mg/kg/day for 13 weeks (ERAUC 3). Enlarged ovaries were seen in one 13 week study in rats at all doses (5, 20 and 60 mg/kg/day), where increased number of mature corpora lutea were present in the high dose group and plasma progesterone levels increased in the mid and high dose groups in week 2 (no difference in progesterone in Week 12 or oestradiol in Week 2 or 12 between treated and control groups). Reduced size and increased number of corpora lutea and liquefactive necrosis were observed in rats at > 20 mg/kg/day for 6 months (ERAUC approximately 0.5) and sparse vascularisation/fibrous tissue between the luteal cells at 80 mg/kg/day (ERAUC 2). Theca cells of sex cord stroma in some animals had pronounced pale staining, clear cytoplasm and a slightly increased number around the corpora lutea or within the ovarian interstitium (sex cord stromal hyperplasia).

VEGF is known to have a role in the development of ovarian follicles and corpus lutea.[[11]](#footnote-12),[[12]](#footnote-13) Most VEGF/VEGFR inhibitors cause ovarian atrophy and impairment of follicular development. The ovarian effects of nintedanib (mainly affecting corpora lutea) might be due to its activities to multiple kinases. Impairment of fertility may be seen in patients treated with nintedanib.

##### Genotoxicity

The potential genotoxicity of nintedanib was investigated using the standard battery of tests, conducted under GLP conditions in accordance with ICH guidelines. All assays were appropriately validated. Appropriate bacterial strains were used in the Ames test and concentrations/doses were appropriate. Nintedanib was not mutagenic in the bacterial mutation assay or clastogenic in vitro (mouse lymphoma cell assay) or in vivo (in the rat micronucleus test). The genotoxic potential of BIBF 1202 was also assessed in in vitro studies (bacterial and mammalian cell assays), and adequate exposure would have also been achieved in the rat micronucleus test, all of which gave negative results.

##### Carcinogenicity

The carcinogenic potential of nintedanib by the oral route was assessed in mice following daily dosing for 103 weeks, and in rats following daily dosing for 104 weeks. The group sizes used (60 to 66/gender) and durations of dosing were appropriate. There were no nintedanib related neoplastic findings in any of the treated groups (≤ 30 mg/kg/day PO in mice and ≤ 10 mg/kg/day PO in rats). The relative exposure at the highest tested dose was moderate in mice (ERAUC 2.5) and low in rats (ERAUC 0.15). Reduced body weight gain and survival was seen in the highest dose in mice. The high dose in rats induced effects on teeth (dentopathy) but there were no significant changes in food consumption and body weight gain. Higher dose could have been dosed in the rat study. This deficiency of the rat study should not preclude approval of the proposed indications since the life expectancy of IPF and NSCLC patients are expected to be short.

##### Reproductive toxicity

Studies on fertility and early embryonic development, embryofetal development and pre /postnatal development in rats and rabbits were submitted in the data package. These studies included dose range finding assessments (non GLP) and main studies (for each study type mentioned above) consistent with regulatory requirements regarding the study design (species, group sizes, timing and duration of treatment).

Placental transfer was not studied. In the pre/postnatal development study in rats, the parent drug and BIBF 1202 were not detected in four day old pups, but low levels of BIBF 1202 glucuronide were detected (mean concentration < 3.35 ng/mL). The presence of the metabolite in the pup plasma could be associated with nintedanib or metabolites in milk and/or placental transfer in utero. No conclusions on the possible placental transfer can be made, but increased embryofetal resorption and fetal malformation (see below) suggest placental transfer.

Excretion of nintedanib and/or metabolites in milk was detected in rats. In female rats, milk concentration of nintedanib 1 hour post dose was approximately 10 fold lower than the plasma concentration but at 6 hours was around 2 fold higher than plasma concentration. AUC of total drug related materials (measured as radioactivity) in milk was slightly higher than in plasma (milk/plasma AUC ratio 1.2). Total estimated nintedanib related radioactivity secreted to milk over 24 h was 0.18 to 0.5% of the administered dose).

Table 6. Exposures to nintedanib in reproductive toxicity studies.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Species | Study | Dose (mg/kg/ day) | AUC0–24 h (ng∙h/mL) | Exposure ratio# | |
| IPF | NSCLC |
| Rat (Wistar Han) | U07-1710-02/07B002 Embryofetal development  GD16 | 30 | 411 | 1.1 | 0.76 |
| 75 | 1025 | 2.8 | 1.9 |
| 180 | 3324 | 9.2 | 6.2 |
| U07-1814 Embryofetal development  GD16 | 5 | 12 | 0.03 | 0.02 |
| 10 | 50 | 0.14 | 0.1 |
| 20 | 305 | 0.84 | 0.56 |
| U13-1923-01/12B017 Embryofetal development  GD16 | 2.5 | BLQ | - | - |
| 5 | BLQ | - | - |
| 10 | 18 | 0.05 | 0.03 |
| U13-2641-01 Pre/postnatal development  Phase 3; LactDay20 | 2.5 | BLQ | - | - |
| 5.0 | 37.6 | 0.10 | 0.07 |
| 10 | 78.8 | 0.22 | 0.15 |
| Rabbit (Him) | U13-1420-01/11B228 Embryofetal development  GD18 | 3 | 49 | 0.13 | 0.1 |
| 7 | 112 | 0.31 | 0.21 |
| 15 | 349 | 0.96 | 0.65 |
| 30 | 923 | 2.5 | 1.7 |
| 75 | 1802 | 5.0 | 3.3 |
| 180 | 2304 | 6.4 | 4.3 |
| U13-1937-01 Embryofetal development  GD18 | 15 | 1920 | 5.3 | 3.6 |
| 30 | 2550 | 7.0 | 4.7 |
| 60 | 5340 | 15 | 9.9 |

# = animal:human plasma AUC0-24 . a = AUC was calculated using the clinical AUC values of 363 and 540 ng∙h/mL for IPF and NSCLS patients, respectively.

Fertility and early embryonic development was studied in rats. Nintedanib had no adverse effect on male fertility at up to 100 mg/kg/day PO for 92 days before mating (ERAUC 3, based on toxicokinetic data of the 3 month repeat dose toxicity study) but female fertility index and gestation index after 2 weeks of treatment before mating were depressed at the highest dose of 100 mg/kg/day PO nintedanib. The exposure in the female fertility study, based on AUC values in the 2 week toxicity study, was only slightly above the clinical exposure. Early resorption of embryos was increased at > 20 mg/kg/day (ERAUC 0.3). Increased early resorptions were also seen in embryofetal development study in rats at 10 mg/kg/day (ERAUC 0.03) and in rabbits at 60 mg/kg/day (ERAUC 10). The NOAEL for effects on female fertility was 3 mg/kg/day PO (ERAUC 0.01).

In a preliminary embryo fetal development study in rats, administration of ≥ 30 mg/kg (ERAUC 0.8) nintedanib from gestation Day 7 to 16 resulted in a complete loss of embryos. In GLP compliant embryofetal development studies, nintedanib PO induced malformations in rats and rabbits. Malformations of the axial skeleton and aortic arch were clearly seen at 10 mg/kg/day in rats, with the frequency of skeletal malformations (above control) also marginally increased at 2.5 mg/kg/day. Elevated incidences of skeletal variations were also detected at 2.5 and 5.0 mg/kg/day. Fetal abnormalities included altered position or size of major arteries (for example carotids, subclavian), flat/thickened ribs and cleft vertebral body (thoracic and cervical). Exposure to the parent drug at the low dose of 2.5 mg/kg/day was below the limit of quantification, but low levels of the metabolite BIBF 1202 and relatively high levels of BIBF 1202 glucuronide (below clinical exposure) were detected.

In rabbits, malformations of the axial skeletal, urogenital and aortic arch/cardiovascular systems were seen at 30 and 60 mg/kg/day PO in the absence of maternal toxicity. External malformations (multiple) were observed at 60 mg/kg, while hernia of the skull and brachydactyly were observed at 15 mg/kg; these uncommon findings were considered to show teratogenic activity at 15 mg/kg (ERAUC 4). Visceral and skeletal abnormalities included cervical/lumbar/thoracic vertebrae anomalies (missing, fused, displaced, cleft, asymmetrical/unilateral ossification), additional or fused ribs, missing or additional major arteries, abnormal heart shape, and missing urogenital organs (kidneys, ureter, uterus, ductus deferens, ovaries).

A pre/postnatal development study in rats (2.5, 5.0 and 10 mg/kg/day nintedanib PO from gestation Day 6 to lactation Day 20) showed smaller litter size, slightly longer gestation length and slightly decreased offspring survival at 10 mg/kg/day and decreased bodyweight and food consumption at > 5 mg/kg. There were no adverse effects associated with treatment on F1 development including sexual maturity, motor activity, learning and memory and bone growth. Drug exposure in the pre/postnatal study was subclinical (ERAUC < 0.3 at 10 mg/kg/day).

Nintedanib was teratogenic and embryofetocidal in rats and rabbits at exposures lower or not significantly higher than those expected at the proposed doses in patients for both indications. Due to this, and to the pharmacological activity of nintedanib (inhibitor of blood vessel growth), nintedanib should be contraindicated in pregnancy.

###### Pregnancy category

The sponsor has proposed Pregnancy Category C[[13]](#footnote-14). The sponsor’s proposed category is not appropriate since malformations were seen in both rats and rabbits at exposure levels lower than anticipated human exposure. Pregnancy Category D[[14]](#footnote-15) is recommended, and is consistent with other VEGF or VEGFR inhibitors.

##### Local tolerance

Local tolerance of the gastrointestinal tract was evaluated during repeated dosing in rats and monkeys and has been discussed under the repeat dose toxicity heading. In rabbits, nintedanib was well tolerated following dermal application to the skin, single administration of the powdered drug in the conjunctival sac, and IV administration. Nintedanib’s haemolytic potential was low, and this is not clinically relevant since the currently proposed route of administration is oral. Nintedanib caused local irritation following intra-arterial or intramuscular administration in rabbits, and paravenous administration in rats. These findings are not considered a concern for the current indication.

##### Phototoxicity

A phototoxicity assay conducted with Balb/c 3T3 cells showed phototoxic potential. Phototoxic reactions on sun exposed skin may occur during clinical use.

##### Paediatric use

Nintedanib is not proposed for paediatric use and no specific studies in juvenile animals were submitted. General repeat dose toxicity studies identified systems that are still developing (bone and teeth) as targets for toxicity.

#### Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for nintedanib detailed in Section SII: Non clinical Part of the Safety Specifications in the sponsor’s draft Risk Management Plan (RMP) for both indications are in general concordance with those of the nonclinical evaluator except for the following:

1. SII.1.1.2 Reproductive and developmental toxicity

Teratogenicity was observed in rats at exposures around 20 fold lower (IPF) or 30 fold lower (NSCLC) than the clinical exposure and in rabbits at exposures 4 to 5 (IPF and NSCLC) times the clinical exposure.

The summary paragraph for NSCLC, which is in line with the TGA nonclinical evaluator’s assessment, is not included in the RMP for IPF.

1. Section ‘SIV.3.3 Pregnant or breastfeeding women’ in the RMP for IPF, does not include the following statement: ‘*Women of childbearing potential should avoid becoming pregnant during treatment with Vargatef and use adequate contraceptive methods. Since the effect of nintedanib on the metabolism and efficacy of contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy*.’

### Nonclinical summary and conclusions

* Nintedanib inhibited PDGFR α/β, FGFR 1-3 as well as VEGFR 1-3 at nanomolar concentrations. Nintedanib inhibited proliferation and migration of human lung fibroblasts and fibroblast to myofibroblast transformation. It inhibited proliferation of VEGF stimulated human umbilical cord endothelial cells (HUVEC) and human skin microvessel endothelial cells, as well as proliferation of PDGF BB stimulated human umbilical cord smooth muscle cells and bovine retinal pericytes. Nintedanib has similar potency in the inhibition of 3 other kinases, namely, FLT3, Lck and Abl, and lower potency against Lyn and Src. Inhibition of FLT3 might be the cause of effects on haematopoietic system observed in repeat dose toxicity studies, while inhibition of other kinases might explain other toxicity findings.
* In mouse and rat animal models of pulmonary fibrosis, nintedanib administration for 30 days was efficacious and tolerated. Nintedanib was more efficacious as a preventer than as a therapeutic against pulmonary fibrosis.
* Nintedanib significantly inhibited tumour growth of NSCLC xenografts in nude mice, and showed additive anti-tumour effects without additional adverse effects, when used in combination with docetaxel, pemetrexed or vinorelbine. Efficacy was also shown in mouse models of other types of tumours (for example head and neck small cell carcinoma, ovarian cancer). Plasma nintedanib concentrations at effective doses in the mouse and rat pharmacology studies for both indications were similar to those in patients.
* The major human metabolite, BIBF 1202 is also a potent inhibitor of the VEGFR-2 and VEGFR-3 kinases, but it shows low activity in the auto phosphorylation of PDGFR and VEGF and FGF stimulated HUVEC proliferation and no significant anti-tumour efficacy (at least in the FaDu tumour model) despite higher drug plasma levels than the parent drug. There were no pharmacology studies on the other major human metabolite, BIBF 1202 glucuronide. Given the high plasma concentration of BIBF 1202 glucuronide in humans (steady state AUC approximately 10 fold higher than the AUC of nintedanib) the absence of pharmacology studies on this metabolite is considered a major deficiency.
* Safety pharmacology studies assessed effects on the cardiovascular, respiratory, renal, gastrointestinal and central nervous systems. No adverse effects were seen on CNS function in mice or rats, respiratory, or renal function in rats. There were no consistent effects on blood pressure in animal species. No significant inhibition of hERG K+ channel tail current was observed at clinically relevant concentrations and no adverse effects were seen in electrocardiograms in repeat dose studies in monkeys. Nintedanib is not predicted to have cardiovascular effects in patients. A slight diuretic effect was seen in rats, but repeat dose toxicity studies showed no consistent renal toxicity in rats and monkeys. Nintedanib slowed GIT movement in rats, and similar effects might occur in patients.
* Oral bioavailability was low in rats, monkeys and humans. Intestinal P-gp activity and first pass metabolism (by ester cleavage) are thought to contribute to the low bioavailability of nintedanib. Protein binding was high in the plasma of animals and humans. Albumin was the major binding protein in human plasma. Tissue distribution of nintedanib and/or its metabolites was rapid and wide in rats. The volume of distribution was greater than total body volume in rats, monkeys and humans, suggesting extensive extravascular distribution. There was limited penetration of the blood brain barrier. Oral bioavailability and excretion of nintedanib may be altered by P-gp inhibitors and inducers.
* Nintedanib was extensively metabolised in all species. Metabolism of nintedanib involved predominantly ester cleavage of the methyl ester to yield BIBF 1202 (M1), and conjugation of BIBF 1202 to 1-O-acylglucuronide of BIBF 1202 (M2) by hepatic UGT1A1 and intestinal UGT1A7, 1A8 and 1A10. Ester cleavage and subsequent glucuronidation was the main clearance pathway in all species despite quantitative differences. Excretion of nintedanib and/or its metabolites was predominantly via the biliary/faecal route in animals and humans.
* Nintedanib and its metabolites, BIBF 1202 and BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes in vitro. Nintedanib is a weak inhibitor of UGT1A1 and UGT2B7, which is of low clinical relevance, and BIBF 1202 is not an inhibitor of these enzymes. BIBF 1202 glucuronide is a substrate of P-gp and BCRP; thus the elimination of BIBF 1202 glucuronide may be altered by MRP2 and BCRP inhibitors or inducers.
* Nintedanib was not a substrate of several uptake transporters (OATP1B1, OATP1B3, OATP2B1 and OCT2), but a substrate of OCT1; however, cellular uptake or binding to cell surface was high without transporters. Thus, the finding is of low clinical relevance. Nintedanib and BIBF 1202 were shown not to be an inhibitor or only a weak inhibitor of uptake transporters (OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, MRP2) or efflux transporters (P-gp, MRP2, BCRP).
* There were no studies investigating the potential activity of BIBF 1202 glucuronide on UGT. Given the high plasma concentration of this metabolite in patients, it is recommended that the activity of BIBF 1202 on UGT be investigated as a post approval requirement.
* Single dose toxicity studies in mice and rats indicated a low order of toxicity.
* Repeat dose toxicity studies by the oral route were conducted in mice (up to 13 weeks), rats (up to 6 months) and monkeys (up to 12 months). Animals were dosed with exposures up to 5 (rats) and 9 (monkeys) times the anticipated clinical AUC for NSCLC (animal/human exposure ratios 1.5 fold higher for the IPF indication). Major toxicity findings are all associated with or secondary to the pharmacological activity of nintedanib (or its metabolites), including reduced red blood cells and effects on lymphoid tissues and bone marrow. The major target organs for nintedanib were the liver (reversible increases in ALT and AST, and haemosiderosis), gastrointestinal tract (vomiting and diarrhoea), bone marrow (hypocellularity with secondary haematological effects for example anaemia), lymphoid organs (lymphoid depletion of the thymus, spleen, lymph nodes), bone (thickening of epithelial growth plates and dentopathy), reproductive tissues (increased number and decreased size of corpora lutea and luteinized follicles in the ovaries) and kidney (hyaline droplets and glomerulopathy).
* Nintedanib was not mutagenic in the bacterial mutation assay or clastogenic in vitro (mouse lymphoma cell assay) or in vivo (in the rat micronucleus test). Metabolite BIBF 1202 was also not mutagenic.
* There were no nintedanib related neoplastic findings in 2 year carcinogenicity studies in mice or rats. Although the relative exposure at the highest tested dose was low, carcinogenicity studies were not essential for the proposed indications because of the short life expectancy of the intended patient groups.
* A standard set of GLP compliant reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). Nintedanib and/or its metabolites were excreted into milk. Placental transfer in rats is suspected but not confirmed. Male fertility and reproductive organs/tissues were not affected, while female fertility was adversely affected (decreases in fertility and gestation indices and increases in early resorption). Malformations of cardiovascular, skeletal and urogenital systems were observed in rats at subclinical exposures and in rabbits at exposures 5 to 7 times the clinical exposure. Smaller litter size, slightly longer gestation length and slightly decreased offspring survival occurred in rats dosed with 10 mg/kg/day (below clinical exposure) nintedanib from gestation Day 6 to lactation Day 20. Pregnancy Category D is considered appropriate since malformations were seen in both rats and rabbits at exposure levels lower than the anticipated human exposures. Based on teratogenicity findings and pharmacological activity of nintedanib, adverse embryofetal effects are predicted in humans.
* Nintedanib was shown to be phototoxic in an in vitro assay. The distribution pattern in pigmented rats resembled closely to that found in albino rats, with both strains showing similar distribution to the skin (similar to blood levels). The distribution pattern in pigmented rats indicated a specific affinity to the melanin containing layer in the eye. Protection of the eyes from the sun during treatment may be necessary. Phototoxic reactions on sun exposed skin and eyes may occur during clinical use.

#### Conclusions and recommendations

The primary pharmacology studies are supportive of the proposed use of the drug as an oral agent for the treatment of IPF and NSCLC. In vitro pharmacokinetic drug interaction studies suggest inducers/inhibitors of P-gp may alter plasma nintedanib concentrations.

Major toxicity findings include:

* hepatotoxicity (increased liver enzymes, haemosiderosis)
* gastrointestinal disturbances (vomiting and diarrhoea)
* lymphoid depletion
* bone marrow toxicity with secondary haematological effects (especially anaemia)
* possible phototoxic reactions on sun exposed skin and eye
* reproductive tissues (effects follicles and corpora lutea in the ovaries)
* kidneys (hyaline droplets and glomerulopathy) (low clinical risk)
* bone (thickening of the growth/epiphyseal plate) and teeth (dentopathy) (not relevant to adult patients).

There was no evidence of genotoxicity or carcinogenicity although exposures in the carcinogenicity studies were low.

Nintedanib is embryolethal and teratogenic in two animal species. Pregnancy category D is recommended. Nintedanib should not be used in pregnancy.

The excretion of nintedanib and/or its metabolites into milk indicates a risk of adverse effects in breast fed infants. Increased postnatal viability was observed in rats.

Provided the above effects are adequately monitored or managed during clinical use, there are no objections on nonclinical grounds to the proposed registration of nintedanib for the proposed indications.

Pharmacological activities and effects on UGT enzymes of the metabolite, BIBF 1202 glucuronide should be investigated as a post approval requirement because of very high plasma levels of this metabolite in humans (approximately 10 fold higher than the parent drug).

The nonclinical evaluator also made recommendations regarding the PI however this is beyond the scope of the AusPAR.

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

### Introduction

Nintedanib is a tyrosine kinase inhibitor (TKI). It blocks the kinase activity of a variety of receptors:

* The vascular endothelial growth factor receptors (VEGFR) -1, -2 and -3
* The platelet derived growth factor receptors (PDGFR) α and β
* The fibroblast growth factor receptors (FGFR) -1, -2 and -3

It also blocks the activity of Flt-3, Lck, Lyn and Src kinases.

The submission seeks approval of the product for two indications:

*In combination with docetaxel, for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy; and*

*The treatment of Idiopathic Pulmonary Fibrosis (IPF) and to slow disease progression.*

The evaluation for each indication for efficacy and safety will be presented sequentially in each section.

#### Clinical rationale

##### Non-small cell lung cancer

Non-small cell lung cancer accounts for approximately 60 to 65% of lung cancers and adenocarcinoma is the most common subtype of NSCLC. Standard first line therapy for most patients with advanced NSCLC is a platinum based doublet chemotherapy regimen. Bevacizumab is also registered in Australia for use in first line treatment in combination with platinum based chemotherapy. Current treatments available for second line use include docetaxel, pemetrexed and erlotinib.

For patients with activating mutations of EGFR, agents available for first line therapy, or for second line therapy following failure of chemotherapy, include gefitinib, erlotinib and afatinib. Crizotinib is registered for the treatment of ALK positive NSCLC.

The proposed use of nintedanib in NSCLC is based on its anti angiogenic effects mediated through inhibition of VEGF and PDGF receptors. Bevacizumab, which acts through inhibition of the VEGF pathway, has already been registered for use in NSCLC. Several other VEGFR inhibitors have been approved for use in other cancers (for example sorafenib, sunitinib, pazopanib).

##### Idiopathic pulmonary fibrosis

Idiopathic Pulmonary Fibrosis (IPF) is a specific form of chronic, progressive interstitial pneumonia of unknown cause. It generally occurs in older adults, is limited to the lungs and is associated with a histological/radiological appearance known as ‘usual interstitial pneumonia (UIP)’. It is a rare condition with a prevalence estimated at between 2 and 29 cases per 100,000. Translated to the Australian population, this would give an approximate prevalence of between 50 and 700 subjects. IPF is a fatal condition with a median survival of 2 to 3 years after diagnosis. Most patients experience a slow, gradual progression with death from respiratory failure.[[15]](#footnote-16)

There are currently no drugs registered in Australia that have been proven to be of benefit in the treatment of IPF. Drugs that have been used include corticosteroids, immunosuppressive agents, colchicine, acetylcysteine, interferon gamma 1b, bosentan and etanercept. The evidence to support the efficacy of any of these agents is weak and current clinical guidelines do not recommend their use.15, [[16]](#footnote-17) A new agent, pirfenidone has in recent years been approved for the treatment of IPF in several foreign markets (including the USA, Europe and Canada). However, at the time of writing of this review it had not been registered in Australia.

According to the sponsor, nonclinical data suggest a potential role of FGF and PDGF signalling in the pathogenesis of IPF. Hence, the clinical rationale is based on nintedanib’s ability to inhibit the receptors for these factors.

#### Guidance

The following European Medicines Agency (EMA) guidelines, which have been adopted by the TGA, are considered relevant to the current application:

* Guideline on evaluation of anticancer medicinal products in man and its appendices 1 and 4.[[17]](#footnote-18)[[18]](#footnote-19)[[19]](#footnote-20)
* Guideline on applications based on a single pivotal trial.[[20]](#footnote-21)
* Guideline on the clinical evaluation of QT interval prolongation.[[21]](#footnote-22)

Compliance with these guidelines is considered in the relevant sections of this report. There is no EMA guideline on drugs intended for IPF.

#### Contents of the clinical dossier

The submission contained the following clinical information:

There were two separate clinical dossiers; one for NSCLC and one for IPF. Together they contained the following:

* 15 clinical pharmacology studies, that primarily provided pharmacokinetic data
* 1 study in renal cell cancer patients that provided data on QT interval
* 3 population pharmacokinetic analyses. Two of these were preliminary and were superseded by the third (U13-1588-01)
* 1 pivotal efficacy/safety study in NSCLC (Study 1199.0013)
* 2 supportive efficacy/safety studies in NSCLC (1199.0014 and 1199.0010)
* 2 pivotal efficacy/safety studies in IPF (1199.0032 and 1199.0034)
* 1 supportive efficacy/safety study in IPF (1199.0030)
* Literature references.

There were several studies included in the submission that were not relevant to the approval being sought. These were primarily early phase studies in which nintedanib was tested in malignancies other than NSCLC and/or studies combining nintedanib with anticancer agents other than docetaxel. These studies have not been evaluated.

There following were also included:

Clinical overview, summary of biopharmaceutics, summary of clinical pharmacology, summary of clinical efficacy and summary of clinical safety (a separate one of each for the two indications), draft Australian PI and Consumer Medicines Information (CMI), draft RMP and various other documents of an administrative data.

#### Paediatric data

The submission did not include paediatric data. As NSCLC and IPF are diseases of adults. This is acceptable.

#### Good clinical practice

The study reports included in the submission all contained assurances that the trials were carried out in compliance with the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice and in accordance with any other applicable regulatory requirements.

### Pharmacokinetics

#### Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies were provided. Table 7 shows the studies relating to each pharmacokinetic topic.

Table 7. Submitted pharmacokinetic studies.

|  |  |  |
| --- | --- | --- |
| PK topic | Subtopic | Study ID |
| PK in healthy adults | Absolute bioavailability | 1199.0075 |
| Mass balance | 1199.0020 |
| Food effect | 1199.0017 |
| Bioequivalence† - Single dose | 1199.0021 |
| PK in special populations | Patients with advanced cancer |  |
| (Single and Multi-dose) | 1199.0001  1199.0002  1199.0003  1199.0019 (Japanese) |
| Patients with NSCLC | 1199.0010 |
| Patients with prostate cancer | 1199.0011 |
| Patients with IPF | 1199.0030 |
| PK interactions | with ketoconazole | 1199.0161 |
| with rifampicin | 1199.0162 |
| with docetaxel | 1199.0004 |
| Population PK analyses | Patients with advanced cancer | Report U11-1279-01 |
| Patients with NSCLC | Report U11-1259-01 |
| Patients with NSCLC or IPF | Report U13-1588-01 |

#### Evaluator’s conclusions on pharmacokinetics

Overall, the PK data in the submission are considered adequate to support registration. Further information on the effect of hepatic impairment would be desirable. An interaction with drugs that elevate gastric pH has not been excluded and a PI statement along these lines should be considered.

### Pharmacodynamics

#### Studies providing pharmacodynamic data

There were no dedicated clinical studies on pharmacodynamics (PD) submitted. Various studies examined PD endpoints and these are listed in Table 8.

Table 8. Studies providing pharmacodynamic data.

|  |  |  |
| --- | --- | --- |
| PD Topic | Subtopic | Study ID |
| Primary Pharmacology | Effect on vasculature in tumours | 1199.0001 1199.0003 |
| Effects on plasma VEGF/bFGF | 1199.0001 |
| Secondary Pharmacology | Effect on QT interval | 1199.0026 |

None of these studies had deficiencies that excluded their results from consideration.

#### Evaluator’s conclusions on pharmacodynamics

Clinical data on PD effects were limited. The dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) data support the proposed mechanism of action.

### Dosage selection for the pivotal studies

#### Non-small cell lung cancer (NSCLC)

In a Phase I study (1199.0004) the maximum tolerated dose of nintedanib, when given in combination with docetaxel was 250 mg BD. However, laboratory results of patients treated at the (maximum tolerated dose) MTD, including the extension cohort, revealed that 4 additional patients experienced transaminase increases of Grade 3 or 4. The recommended dose of nintedanib in combination with docetaxel and prednisone was therefore considered to be 200 mg BD

#### Idiopathic pulmonary fibrosis (IPF)

In a Phase II study (1199.0030) a dose of 150 mg BD was found to produce beneficial effects on Forced vital capacity (FVC). Lower doses did not show such beneficial effects. Higher doses have not been studied.

### Efficacy non-small cell lung cancer

#### Studies providing efficacy data (NSCLC)

Pivotal efficacy study

* Study 1199.0013 (‘LUME-Lung 1’)

Other efficacy studies

* Study 1199.0014 (‘LUME-Lung 2’)
* Study 1199.0010

For details of the studies please see Attachment 2.

#### Evaluator’s conclusions on efficacy (NSCLC)

The pivotal study was well designed and conducted. It complied with the requirements of the EMA guidelines adopted by the TGA. The trial demonstrated that nintedanib has activity in the treatment of NSCLC as evidenced by statistically significant effects on such endpoints as disease control rate and tumour size.

The primary endpoint was progression free survival (PFS). Although a statistically significant result was obtained, the effect was of dubious clinical significance, as median PFS was only increased by 0.7 months (approximately 3 weeks). There was also no survival benefit in the overall population.

The application rests on the finding of an increase in overall survival (a secondary endpoint) in the subgroup of patients with adenocarcinoma. The analysis for survival in the adenocarcinoma subpopulation was defined prospectively but after the results of the initial PFS analysis was known. For a group with a median survival of only 10.3 months, an increase of 2.3 months would be important. The increase in survival is therefore considered to be clinically significant.

The application for the NSCLC indication is based on a single pivotal study. The TGA has adopted an EMA guideline20 that addresses the situation where regulatory approval is being sought on the basis of a single pivotal study. This guideline states that the results of such a study needs to be ‘*exceptionally compelling*’ and it sets out a number of ‘*prerequisites*’ for the study. One of the prerequisites is that ‘*statistical significance considerably stronger than p < 0.05 is usually required.*’ The p-value obtained in the overall survival (OS) analysis in the adenocarcinoma population was 0.0359.

On balance, given the magnitude of the survival benefit, it is considered that the evidence for efficacy is adequate to support registration.

The study did not collect data on NSCLC tumour biomarkers such as EGFR mutation status or ALK positivity. The place of nintedanib in the therapy in the treatment of tumours with these characteristics is therefore unknown.

### Efficacy idiopathic pulmonary fibrosis (IPF)

#### Studies providing efficacy data (IPF)

The main evidence for efficacy comes from two Phase III, randomised, double blind and placebo controlled studies (1199.0032 (‘INPULSIS 1’) and 1199.0034 (‘INPULSIS 2’)). These two studies had essentially an identical design. Supportive evidence was provided by one Phase II dose ranging study (1199.0030).

For further details of the studies please see Attachment 2.

#### Evaluator’s conclusions on efficacy (IPF)

The two pivotal studies were well designed and well conducted. They have demonstrated that nintedanib has activity in the treatment of IPF, with effects on FVC that were highly statistically significant compared to placebo. There was also inconsistent evidence that the drug may reduce the incidence of acute exacerbations of the disease. Overall there was no convincing evidence that nintedanib resulted in favourable effects on quality of life or patient symptoms such as dyspnoea and cough.

FVC is a surrogate endpoint for efficacy, as it does not measure effects that are of direct benefit to patients (for example improvement in symptoms, function or life expectancy). Appropriate endpoints for Phase III studies in IPF have been the subject of debate in the literature in recent years,[[22]](#footnote-23),[[23]](#footnote-24) with some authors arguing that hard endpoints such as mortality should be used and others supporting the use of surrogate endpoints such as FVC. No consensus has been reached. There are no specific regulatory guidelines on the issue. However it is noted that overseas regulators (for example FDA and EMA) have approved pirfenidone and nintedanib based on studies that demonstrated a benefit on FVC.

The pivotal studies in this submission demonstrated that nintedanib significantly reduces the proportion of patients experiencing a 5% or 10% decline in FVC. A decline of 5 to 10% in FVC has been associated with an increased risk of death in the following 12 months.[[24]](#footnote-25)

IPF is a fatal condition and currently there are no therapies registered in Australia that have been shown to be effective. Overall it is considered that the evidence for efficacy of nintedanib in the treatment of IPF is sufficient to support registration. The pivotal studies did not include patients with more severe disease. Although there is no agreed scheme for classifying disease severity of IPF, the indication should be restricted to the population studied. This could be achieved by limiting the indication to ‘*mild to moderate*’ IPF with explanatory text in the clinical trials section of the PI.

### Safety

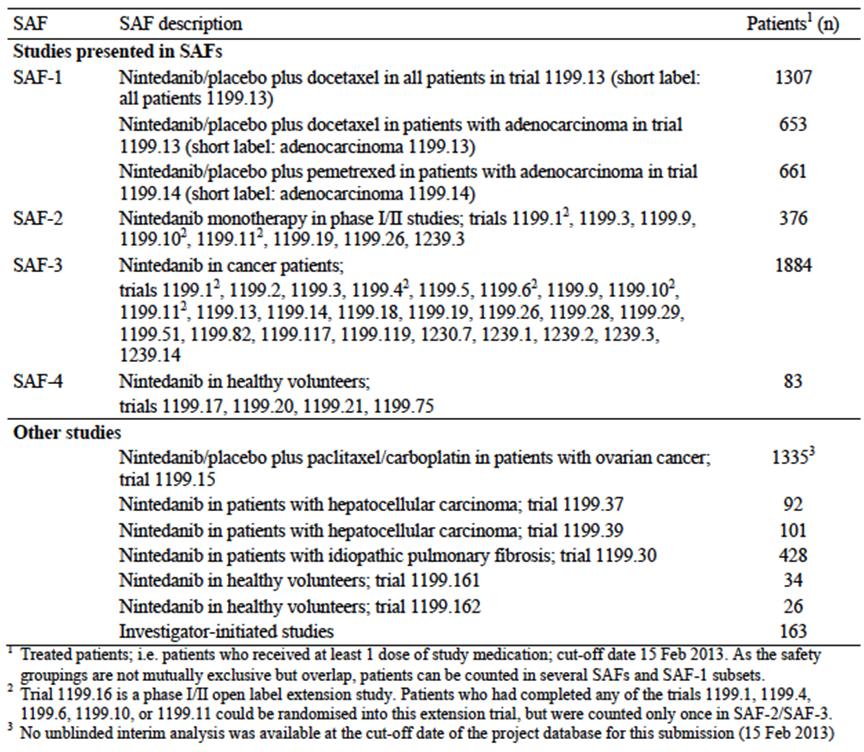
#### Studies providing safety data (NSCLC)

Four ‘safety analysis sets’ (SAFs) were defined:

* SAF-1 included data from the two Phase III randomised, double blind placebo controlled trials 1199.0013 and 1199.0014
* SAF-2 included data from patients treated with nintedanib monotherapy in Phase I/II trials
* SAF-3 included data from patients with cancer
* SAF-4 included data from studies in healthy volunteers.

The trials included in SAFs-1 to 3 were not mutually exclusive but overlapped. A summary of the studies included in these safety sets is shown in Table 9.

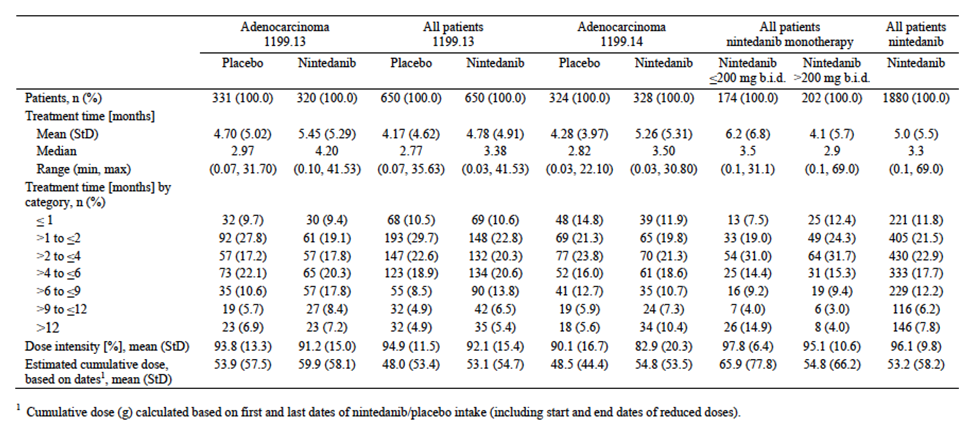
Table 9. NSCLC studies - safety analysis sets.



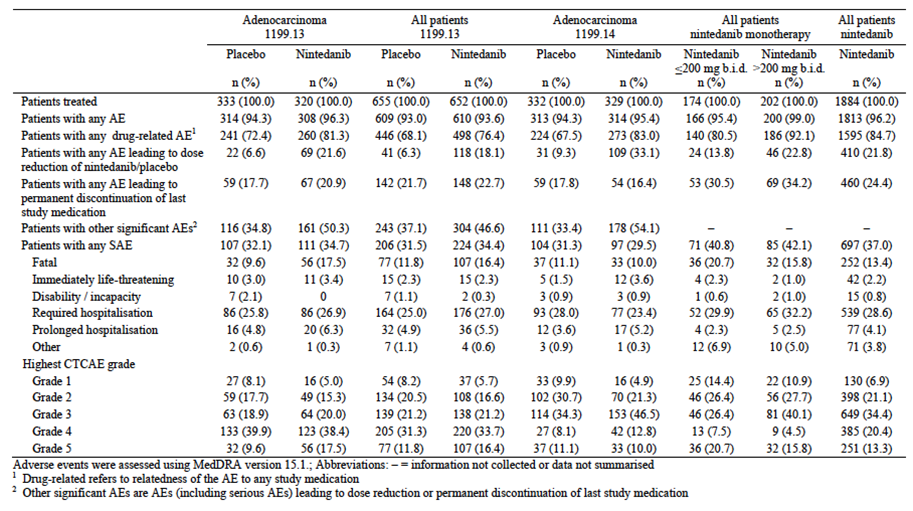
#### Patient exposure (NSCLC)

Exposure to nintedanib and placebo is summarised in Table 10. In total, 1,880 cancer subjects were exposed to nintedanib. Average duration of exposure was short (for example median = 3.38 months in Study 1199.0013). A total of 146 cancer subjects had received nintedanib for periods > 12 months. Dose intensity was generally > 90%. The overall safety profile in NSLC studies is shown in Table 11.

Table 10. NSCLC studies – Exposure. Duration of nintedanib/placebo treatment in Phase III trials 1199.13 and 1199.14 (SAF-1) in nintedanib Phase I/II monotherapy trials (SAF-2) and in all patients with cancer treated with nintedanib.



**Table 11. NSCLC studies – Overall safety profile.**



#### Studies providing safety data (IPF)

Studies conducted in IPF patients are summarised in Figure 3 and Table 12. Including the open extension trials, approximately 1,350 unique subjects received nintedanib in the submitted studies. Review of safety data in this report will focus on the two pivotal Phase III Studies, 1199.0032 and 1199.0034, and the Phase II Study 1199.0030 (150 mg BD dose group). These three studies were double blind, placebo controlled trials of 52 weeks duration.

Figure 3. Studies in IPF subjects.

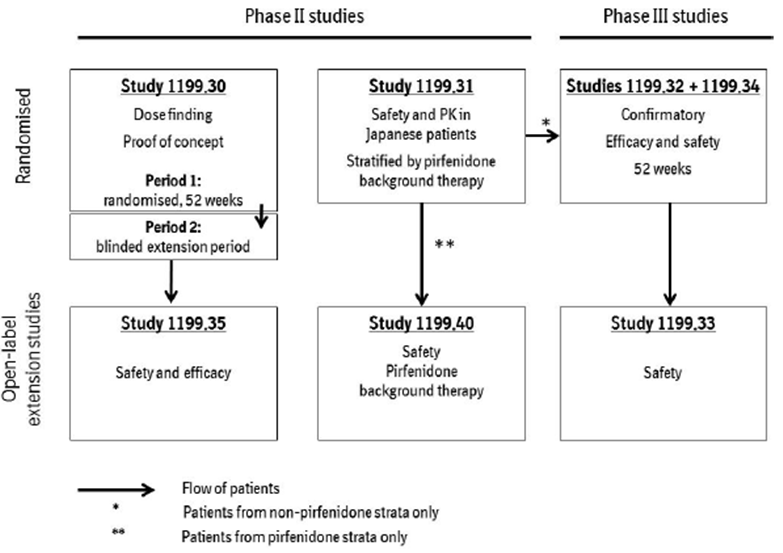
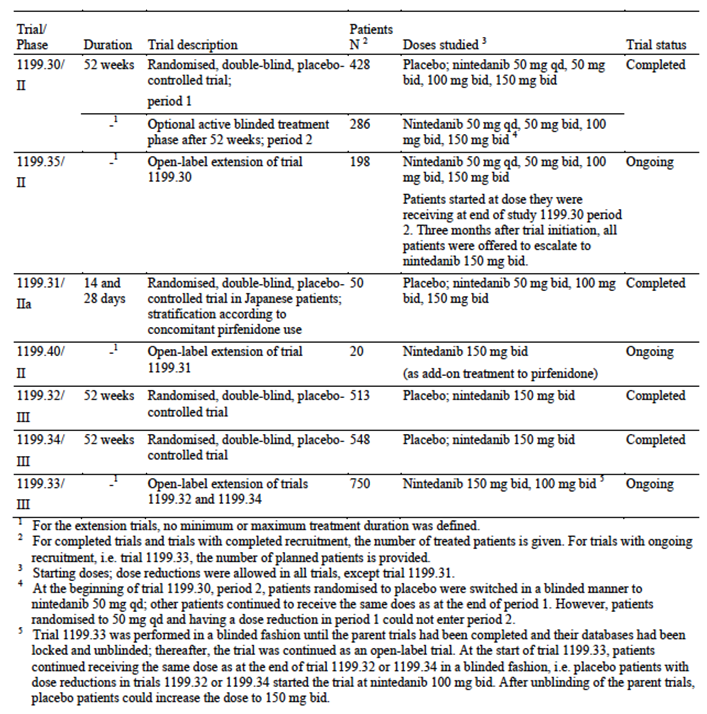


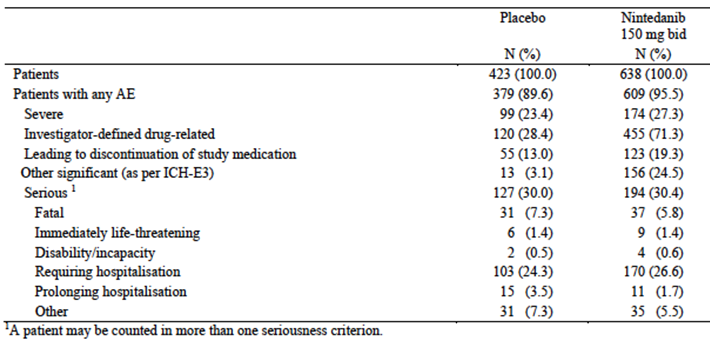
Table 12. Studies in IPF subjects.



#### Patient exposure (IPF)

Extent of exposure in the pivotal studies was provided. Average duration of nintedanib exposure was 10.29 months and 129 subjects received the drug for over 12 months. Extent of exposure in Study 1199.0030 was provided. Average duration of nintedanib exposure was 9.5 months. A summary of adverse events (AEs) in Studies 1199.0032 and 1199.0034 is shown in Table 13.

Table 13. Studies 1199.0032 and 1199.0034 – overall summary of AEs.



#### Safety issues with the potential for major regulatory impact

##### Liver toxicity

As described above, hepatotoxicity is a common adverse event with nintedanib. The hepatotoxicity observed in the NSCLC and IPF studies was reversible. There was one case in a NSCLC patient that met the criteria for Hy’s law, which is predictive of a capacity for the drug to cause severe drug induced liver injury (DILI). The relevant FDA guideline[[25]](#footnote-26) contains the following text:

‘*Finding one Hy’s Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population.’*

Nintedanib may therefore be associated with a risk of severe DILI. Prior to a decision on registration it would be prudent to seek updated information from the sponsor on any further cases that met Hy’s law criteria, or cases of hepatic failure.

##### Haematological toxicity

When co administered with docetaxel, nintedanib caused an increase in the incidence of neutropaenia. In the pivotal study there were 2 reports of pancytopenia in the nintedanib group and 1 in the placebo group. In the IPF studies the incidence of cytopaenias was not increased in the nintedanib arm and there were no reports of pancytopenia.

##### Serious skin reactions

In the NSCLC studies, nintedanib treatment was associated with a small increase in the incidence of serious skin reactions, compared to placebo. There were no reports of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). In the IPF studies, the incidence of serious skin reactions was comparable in the two arms. There were no reports of SJS or TEN.

##### Cardiovascular safety

In the NSCLC studies, nintedanib treatment was associated with a slight increase in the incidence of venous thromboembolic events. There was no consistent increase in the incidence of cardiac events. In the IPF studies there was an increased incidence of myocardial infarction with nintedanib. Otherwise there was no increase in cardiovascular events. In a study conducted in subjects with renal cell cancer, nintedanib did not have an effect on QT interval.

##### Unwanted immunological events

In the NSCLC studies there was no increase in the incidence of anaphylactic reactions with nintedanib. In the IPF studies there were no cases of serious immunological events such as anaphylaxis.

#### Other safety issues

##### Safety in special populations

Among nintedanib treated subjects, females experienced higher rates of hepatotoxicity than males. Asian subjects also experienced higher rates of hepatotoxicity compared to non-Asian subjects. The incidence of SAEs increased with increasing age.

###### Post marketing data

No post marketing experience data were included in the submission

###### Evaluator’s conclusions on safety

In both the NSCLC and IPF populations the most common adverse effects associated with nintedanib were:

* Gastrointestinal (diarrhoea, nausea, vomiting, abdominal pain, decreased appetite, etcetera). These events were very common. However, compared to placebo there was only a small increase in the incidence of severe or life threatening gastrointestinal events.
* Hepatotoxicity. Abnormal liver function tests (LFTs) were very common. The abnormalities were reversible and no cases of severe drug induced liver injury were observed in the submitted studies. However one patient developed LFT abnormalities that fulfilled the criteria for Hy’s law.

Hypertension also occurred more frequently with nintedanib treatment in both populations.

In the NSCLC population, where nintedanib was used in combination with chemotherapy, the following toxicities were also more common with nintedanib:

* Venous thromboembolic events
* Neutropenia, febrile neutropenia and fatal sepsis
* Serious skin reactions.

In the IPF population, the following toxicities were also more common with nintedanib:

* Arterial thromboembolic events, most commonly myocardial infarction
* Decreased weight
* Bleeding events
* GI perforation.

Many of these toxicities are consistent with those previously observed for drugs which interrupt the VEGF/VEGFR pathway.

In the pivotal study in NSCLC, nintedanib treatment resulted in only a small increase in the proportion of patients who experienced a serious AE (versus placebo) (34.4% nintedanib versus 31.5% placebo) or a Grade ≥ 3 AE (71.3% versus 64.3%). There was an increase in the incidence of fatal AEs in the nintedanib arm (16.4% versus 11.8%). However most of these were related to disease progression and of the remainder, only an increased incidence of fatal sepsis (7 versus 1 cases) appeared related to nintedanib. The overall increase in toxicity produced by the addition of nintedanib to docetaxel is considered modest. The proportion of subjects who discontinued treatment due to AEs was only slightly increased in the nintedanib arm (22.7% versus 21.7%). This suggests that nintedanib toxicity is manageable with dose reductions and interruptions.

In the pivotal IPF studies, nintedanib treatment resulted in only a small increase in the overall incidence of adverse events (versus placebo) (95.5% nintedanib versus 89.6% placebo) with no increase in the incidence of serious AEs (30.4% versus 30.0%) and a small increase in the incidence of AEs classified as severe (27.3% versus 23.4%). There was no increase in the incidence of fatal AEs. The overall toxicity of the drug in IPF can therefore be considered to be modest. The proportion of subjects who had to discontinue treatment due to AES was modestly increased (19.3% versus 13.0%).

### First round benefit-risk assessment

#### First round assessment of benefits

The benefits of nintedanib in the treatment of NSCLC with adenocarcinoma histology, in combination with docetaxel, are:

* A decreased risk of death with an increase in median survival of approximately 2.3 months, when compared to docetaxel monotherapy.

The benefits of nintedanib in the treatment of IPF are:

* A delay in disease progression, manifested by improved FVC compared to placebo.

#### First round assessment of risks

The risks of nintedanib in the treatment of NSCLC with adenocarcinoma histology, in combination with docetaxel, are:

* Gastrointestinal toxicity
* Hepatotoxicity
* Hypertension
* Venous thromboembolic events
* Neutropenia leading to febrile neutropenia and sepsis
* Serious skin reactions.

The risks of nintedanib in the treatment of IPF are:

* Gastrointestinal toxicity
* Hepatotoxicity
* Hypertension;
* Arterial thromboembolic events such as myocardial infarction
* Decreased weight
* Bleeding events
* GI perforation.

#### First round assessment of benefit-risk balance

For the treatment of NSCLC with adenocarcinoma histology, in combination with docetaxel the benefits of nintedanib are clinically significant with an average prolongation of survival of approximately two months in a population of patients with an average survival of only 10 months. This benefit is considered to outweigh the modest additional toxicity that the drug causes. Therefore the benefit-risk balance of nintedanib in this setting is considered favourable.

For the treatment of mild to moderate IPF, the benefits of nintedanib are clinically significant, with a delay in the progression of a life threatening condition, for which there are currently no effective therapies available in Australia. This benefit is considered to outweigh the modest toxicity that the drug produces. The benefit-risk balance of nintedanib in this setting is therefore considered favourable.

### First round recommendation regarding authorisation

It is recommended that the application be approved for the following indications:

* *In combination with docetaxel, for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy; and*
* *The treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF).*

### Clinical questions

#### Pharmacokinetics

Please provide a summary of any available data from the ongoing Studies 1199.0037, 1199.0039 and 1199.0120 on the effect of hepatic impairment on the PK of nintedanib.

#### Safety

The submitted studies identified one case that met the criteria for Hy’s law, which is predictive of severe drug induced liver injury. Please provide details of any further cases that have been identified, as well as any new cases of hepatic failure.

### Second round evaluation of clinical data submitted in response to questions

#### Effect of hepatic impairment on PK of nintedanib

The sponsor indicated that PK data from the three identified studies are not yet available. The sponsor also identified another relevant study (Study 1199.0200). This study is a single dose study in volunteers with hepatic impairment (Child Pugh A and B) who are otherwise healthy, and matched healthy controls. A summary report of these studies is expected to be available in July 2015.

#### Drug induced liver injury

##### Hy’s law cases

For oncology subjects, the sponsor provided updated data from the previously submitted oncology studies together with data from an interim safety analysis of an ongoing study in ovarian cancer (Study 1199.0015). A total of approximately 2,800 subjects had been treated in these studies. One additional case was identified (subject [information redacted] in Study 1199.0015) that fulfilled the criteria for Hy’s law, without any other identifiable cause. The total number of such cases therefore is two.

For IPF subjects, no cases fulfilling Hy’s law criteria were identified in an updated safety analysis of ongoing IPF studies. There have therefore been no cases reported among IPF subjects.

##### Hepatic failure

The sponsor searched its safety databases with a standardised MedDRA query (SMQ) entitled ‘*hepatic failure, fibrosis and cirrhosis, and other liver damage related conditions, broad*’. This SMQ includes several terms that do not necessarily indicate severe liver dysfunction (for example ‘hepatotoxicity’, ‘liver disorder’, ‘hepatocellular injury’ etcetera.). The sponsor presented a review of the cases retrieved. This demonstrated that none of the cases met stringent criteria for liver failure (increases in transaminases with hepatocellular jaundice and subsequent international normalised ratio (INR) increase, hypoproteinaemia, encephalopathy, coma, death). In most cases the AEs were considered related to underlying malignancy. None were consistent with severe DILI induced by nintedanib.

### Second round benefit-risk assessment

#### Second round assessment of benefits

No new clinical efficacy information was submitted in response to questions. Accordingly, the benefits of nintedanib are unchanged from those identified in the first round assessment of benefits.

#### Second round assessment of risks

The sponsor identified one additional patient with LFT abnormalities meeting Hy’s Law criteria, without any identifiable cause (apart from nintedanib). A total of two such cases have been identified, both in subjects with advanced malignancy. It is therefore possible that nintedanib may be associated with severe DILI, although no such cases have been reported. The issue will need to be monitored closely in the post market setting.

After consideration of the responses to clinical questions, the risks of nintedanib in the proposed usage are essentially unchanged from those identified in the first round assessment of risks.

#### Second round assessment of benefit-risk balance

Both advanced NSCLC and IPF are serious life threatening conditions. Even if nintedanib were to be associated with rare cases of severe DILI, the overall benefit-risk balance of the drug is still considered favourable.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted the following Risk Management Plans (RMPs)

* Vargatef EU-RMP version 1.2 dated 19 May 2014 (data lock point 15 February 2013) with Australian Specific Annex version 1.0 dated 11 July 2014
* Ofev EU-RMP Version 1.0 dated 9 April 2014 (data lock point 26 November 2013) and Australian Specific Annex version 1.0 dated 7 July 2014

which were reviewed by the RMP evaluator.

The two sets of RMP documents submitted by the sponsor are for the two products with two different trade names used to treat two types of indications. In line with this, the following sections of the evaluation report will consider relevant parts of the two sets of RMPs separately, namely the RMP for Vargatef (for the treatment of NSCLC) and the RMP for Ofev (for the treatment of IPF). However, there is only one PI document (for Australia) that includes information for both Vargatef and Ofev.

#### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Tables 14 and 15.

Table 14. Summary of ongoing safety concerns for Vargatef (for the treatment of NSCLC).

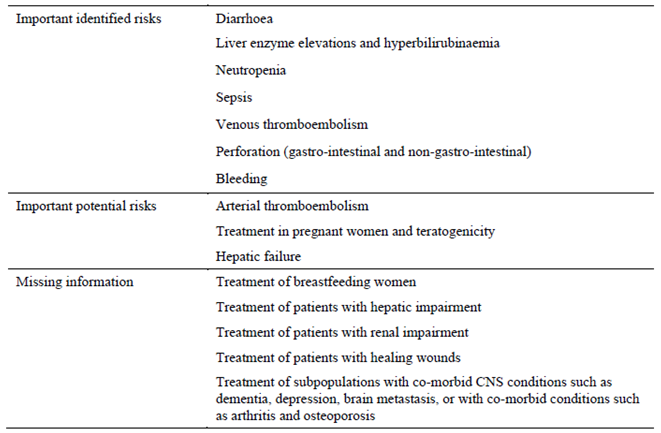
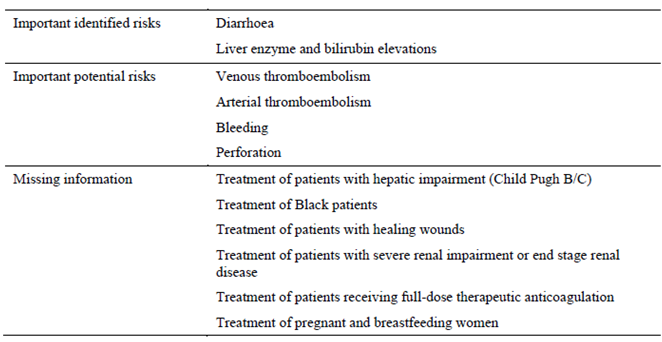


Table 15. Summary of ongoing safety concerns for Ofev (for the treatment of IPF).



#### Pharmacovigilance plan

##### Proposed pharmacovigilance activities

###### Vargatef (for the treatment of NSCLC)

The sponsor has advised:

Routine pharmacovigilance is considered appropriate. This will include periodic monitoring of the safety database. Post approval pharmacovigilance will aim to identify changes in the adverse event characteristics and detect currently unanticipated new aspects. Risks, including missing information, will be monitored and reported in periodic safety updates. Specific action will be taken if warranted based on newly emerging results.

The sponsor also claims that ‘Vargatef is subject to additional monitoring in the European Union.’ (Part V.1, EU-RMP for Vargatef).

###### Ofev (for the treatment of IPF)

The sponsor has advised:

Routine pharmacovigilance is considered appropriate (as described for NSCLC).

In addition, a trial of nintedanib in volunteers with hepatic impairment (Trial 1199.200) is planned, to address the item missing information, ‘treatment in patients with hepatic impairment’

*Evaluator’s comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones*

The sponsor should submit the protocol for Trial 1199.200 to the TGA for review once it becomes available.

#### Risk minimisation activities

##### Vargatef (for the treatment of NSCLC)

The sponsor has proposed routine risk minimisation through product labelling to mitigate all the ongoing safety concerns for Vargatef.

##### Ofev (for the treatment of IPF)

Routine risk minimisation through product labelling has been proposed by the sponsor to mitigate all the ongoing safety concerns for Ofev.

**Evaluator’s comment**: The sponsor’s comment is acceptable.

Liver enzyme elevation and hyper bilirubinaemia is an identified risk for both Vargatef and Ofev. The product label approved by the US FDA for Ofev contains the following detailed instruction on liver function monitoring:

‘*Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter and as clinically indicated. Dosage modifications or interruption may be necessary for liver enzyme elevations.*’

In comparison, the proposed Australian PI provides a more general advice on the frequency of monitoring as follows:

‘*Hepatic transaminase and bilirubin levels should be investigated before the initiation of treatment with TRADENAME and periodically thereafter (for example at each patient visit) or as clinically indicated.*’

It is recommended that the Delegate considers this instruction in the context of improvement of the safety.

#### Reconciliation of issues outlined in the RMP report

Table 16 summarises the first round evaluation of the RMP, the sponsor’s responses to issues raised by the evaluator and the evaluator’s evaluation of the sponsor’s responses.

Table 16. Reconciliation of issues outlined in the RMP evaluation.

|  |  |  |
| --- | --- | --- |
| Recommendation in RMP evaluation report | Sponsor’s response | RMP evaluator’s comment |
| 1. Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA’s request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP. | The Evaluator’s comment has been noted. | n/a |
| 2. The sponsor should explain why drug interaction with P‑gp and CYP3A4 inhibitors/inducers are not considered safety risks for nintedanib or these should be added to the safety concern list in the ASAs for both Vargatef and Ofev. | Preclinical in vitro data showed that nintedanib is a substrate of P‑gp. Both in vitro and in vivo, nintedanib was not metabolised to a relevant extent by the CYP 450 system.  CYP 3A4 perpetrators are summarised for the proposed label together with P-gp perpetrators because the overlap in CYP and P‑gp inhibitors respective inducers is substantial and because the chosen model inhibitor/inducer in the Phase I studies (ketoconazole and rifampicin, respectively) were dual perpetrators. Based on the metabolic properties of nintedanib, a relevant influence on the PK of nintedanib by sole perpetrators of CYP 3A4 without P-gp component is, however, not expected.  In a dedicated drug-drug interaction (DDI) study in healthy volunteers co administration with the P-gp and CYP 3A4 inhibitor ketoconazole led to increased exposure to nintedanib: 1.61 fold based on AUC and 1.79 fold based on Cmax. Thus, if administered concomitantly with nintedanib, potent P-gp inhibitors (for example ketoconazole, erythromycin) may increase nintedanib exposure.  In a dedicated DDI study in healthy volunteers co-administration with the P-gp and CYP3A4 inducer rifampicin decreased exposure to nintedanib to 50.1% based on AUC and to 59.8% based on Cmax. Thus, if administered concomitantly with nintedanib, potent P-gp inducers (for example rifampicin, carbamazepine, phenytoin, St. John’s Wort) may decrease nintedanib exposure. Co administration with P-gp inducers which resulted in decreased exposure to nintedanib is thus not considered to convey a safety risk.  The effect of the concomitant use of P-gp inhibitors and inducers with nintedanib in the clinical setting in patients with IPF and NSCLC was investigated by the Phase II/III PopPK analysis and in the PK analyses of Trials 1199.32 and 1199.34. No significant influence of P-gp inducers or P-gp inhibitors on nintedanib exposure was identified in any of these analyses.  Analyses based on data from the clinical setting as used for the PopPK analysis and the PK investigations of Phase III data may better reflect clinical routine compared to a dedicated Phase I DDI study, even if there are certain limitations as the dose taken, the route of administration, and time of intake for P-gp inducers and P‑gp inhibitors relative to nintedanib were not recorded. Also, the number of patients using P-gp inducers or strong P-gp inhibitors, that is model inhibitors of P-gp as specified in regulatory DDI guidelines, was low: less than 8% of PK observations were associated with concomitant intake of a P-gp inducer and P-gp inhibitor in the PopPK analysis, respectively.  Based on the totality of the available data, the sponsor suggests that the current description in the DDI section of the proposed label provides appropriate guidance for the prescriber. Management of the side effects potentially resulting from increased exposure to nintedanib when given in combination with a CYP 3A4/P-gp inhibitor does not require specific measures; the general monitoring rules and dose adaptation scheme as recommended in the label should be followed. Consequently, the sponsor believes that co administration with CYP 3A4/P-gp perpetrators is not to be considered a safety risk for nintedanib and should not be added to the ASA for both NSCLC and IPF indications. | The sponsor’s response appears to reflect the following information provided in the proposed Australian PI:  *‘Nintedanib is a substrate of P-gp (see Pharmacology, Pharmacokinetics). Co-administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1.61 fold based on AUC and 1.83 fold based on* Cmax *in a dedicated drug-drug interaction study.*  *In a drug-drug interaction study with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60.3% based on* Cmax *upon co-administration with rifampicin compared to administration of nintedanib alone.*  *If co administered with OFEV, potent P‑gp inhibitors (for example ketoconazole or erythromycin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with OFEV (see Dosage and Administration).*  *Potent P-gp inducers (for example rifampicin, carbamazepine, phenytoin, and St. John’s Wort) may decrease exposure to nintedanib. Selection of an alternate concomitant medication with no or minimal P-gp induction potential should be considered.’*  Therefore, the evaluator considers that the potential safety risk related to drug interaction with P-gp inhibitors/inducers has been adequately addressed. |
| 3. Subject to the evaluation outcomes of the nonclinical and clinical aspects of the safety specifications (SS), it is recommended that ‘treatment of patients receiving full dose therapeutic anticoagulation’ should be added to the RMP for Vargatef. | There are no data available for patients receiving full dose therapeutic anticoagulation treatment prior to start of treatment with nintedanib. Patients in Study 1199.13 who developed thromboembolic events during treatment and who required full dose anticoagulant treatment were allowed to continue receiving nintedanib, and did not show an increased frequency of bleeding events.  However, the number of patients receiving concomitant therapeutic anticoagulation with acenocoumarol, phenprocoumon, warfarin or warfarin sodium was small, and a definitive safety conclusion cannot be made regarding the concomitant use of therapeutic anticoagulation with nintedanib.  Therefore the sponsor agrees to add ‘*treatment of patients receiving full dose therapeutic anticoagulation*’ in the ASA for NSCLC as missing information. | The sponsor’s response is acceptable. |
| 4. Tyrosine kinase inhibitors are seen as promising treatment options for different types of solid tumours. Trial 1199.15 U09-1763 is an example of investigating nintedanib for the treatment of ovarian cancer. In addition, clinical trials are also underway to investigate the combination treatment of nintedanib with drugs other than docetaxel. Therefore, the off label use of nintedanib is highly likely. The sponsor should add ‘off label use’ as ‘missing information’ in the ASA for both Vargatef and Ofev. | Oncology  Several angiogenesis inhibitors, such as bevacizumab, sunitinib and sorafenib are currently approved for the treatment of a broad spectrum of different oncological indications. Therefore, off label use of nintedanib in patients with cancers for which alternative angiogenesis inhibitors are approved and available is considered unlikely.  Efficacy and safety of nintedanib in combination with docetaxel have been established for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first line chemotherapy. Nintedanib is in development in further oncology indications.  The sponsor does not encourage the use of nintedanib outside the terms of an approved indication. However such use may occur particularly in cancer patients for whom treatment options are exhausted. Use in these patients is frequently based on published clinical data (or standard treatment guidelines).  Information of off label use with and without ADR will be collected, and periodically assessed using routine pharmacovigilance activities. The sponsor does not intend to add ‘off label use’ as missing information in the ASA for NSCLC.  IPF  IPF is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause. IPF occurs primarily in older adults, is limited to the lungs, and is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). The diagnosis of IPF requires both exclusion of other known causes of interstitial lung disease (ILD) (for example, domestic and occupational environmental exposures, connective tissue disease, and drug toxicity) and the presence of a UIP pattern on high resolution computed tomography in patients not subjected to surgical lung biopsy.  Among the 7 idiopathic interstitial pneumonias (IIP) IPF is the most common disease and has the worst prognosis and. In contrast to the progressive, irreversible disease of IPF the off label use of nintedanib in other IIP with less aggressive behaviour (for example idiopathic nonspecific interstitial pneumonia; NSIP) is considered unlikely by the sponsor. The sponsor therefore does not intend to add ‘off label use’ as missing information in the ASA for IPF. | The sponsor’s response is acceptable. |
| 5. The pharmacovigilance and risk minimisation sections should be updated accordingly to provide plans for managing these safety issues. | The additional issues were identified on the EMA web site by the TGA. The additional issues represent the difference between the RMP version initially submitted (to EMA as well as TGA) in September 2013 and the finally agreed version of the RMP v1.4 as a result of the EU marketing authorisation approval process in November 2014.  Please note that in December 2014 the final nonclinical trial report for Study PK140T (in vitro evaluation of the interaction of nintedanib with human OAT transporters) was submitted to EMA in order to fulfil a post authorisation measure included as additional activity in the RMP. The RMP was revised accordingly. Approval of RMP v2.1 was received 26 Feb 2015.  The additional issues, that is Hypertension, Cardiac failure, QT prolongation, Use in low weight patients (< 50 kg), and Interaction with OAT1 and OAT3 are addressed in the most recent update of the RMP (v2.1).  The most recent EU RMPs for IPF and for NSCLC, which includes the additional issues mentioned above are provided.  Concerning the use of P-gp and CYP3A4 inhibitors/inducers and the potential off label use of nintedanib please refer to the sponsor’s responses to RMP Question 2 and RMP Question 4. The sponsor does not consider necessary the inclusion of the concomitant use of P-gp and CYP3A4 inhibitors/inducers as safety risks for nintedanib. In addition, the off label use of nintedanib in IPF is considered unlikely by the sponsor and thus not warranting its inclusion as missing information in the ASA. | The sponsor’s response is acceptable. |
| 6. It is noted that the following safety concerns have been added to the updated EU-RMP version 1.4 for Vargatef  Hypertension;  Cardiac failure;  QT prolongation;  Use in low weight patients (< 50 kg); and  Interaction with OAT1 and OAT3.  The sponsor should submit the EU-RMP version 1.4 for Vargatef and the approved EU-RMP for Ofev to the TGA. | The safety concerns listed above, that is hypertension, cardiac failure, QT prolongation, Use in low weight patients (< 50 kg), and Interaction with organic anion transporter 1 (OAT1) and OAT3 are addressed in the most recent update of the NSCLC RMP (v2.1). The current NSCLC RMP (v2.1) and IPF RMP (v1.2), as approved by the EMA, are provided.  NSCLC RMP: changes between v1.2 and v2.1 (last approved version)  RMP update v1.3 (according to EMA day 150 questions):  Addition of important identified risk ‘Hypertension’  Addition of important potential risks ‘Cardiac failure’ and ‘QT prolongation’  RMP update v1.4 (according to EMA request):  Addition of missing information ‘Patients weighing < 50 kg’ and ‘In vitro inhibitory potential on OAT1 and OAT3’ according to EMA requests within Committee for Medicinal Products for Human Use (CHMP) evaluation  RMP update v2.1 (PV milestone reached: results of PK study PK1407T):  Demotion of missing information ‘In vitro inhibitory potential on OAT1 and OAT3’ based on study results from the in vitro Study PK1407T IPF RMP: changes between v1.0 and v1.2 (last approved version)  RMP update v1.1 (response to EMA d120 questions):  Addition of the important potential risks ‘Hepatic failure’ and ‘Treatment of pregnant women and teratogenicity’  Demotion of the missing information ‘Treatment of pregnant and breastfeeding women’  Addition of the missing information ‘Interaction of OFEV with hormonal contraceptives’ and ‘Concomitant treatment with pirfenidone’  RMP update v1.2 (according to EMA request within CHMP evaluation phase):  Addition of the important potential risks ‘Cardiac failure’ and ‘QT prolongation’  Addition of the missing information ‘Treatment of breastfeeding women’ | The sponsor’s response is acceptable. |
| 7. The sponsor should submit the protocol for Trial 1199.200 to the TGA for review once it becomes available. | The referenced protocol with EudraCT No.: 2014-000690-39 and the sponsor’s Trial No.: 1199.200 ‘Pharmacokinetics, safety and tolerability of nintedanib single oral dose in male and female patients with different degrees of hepatic impairment (Child-Pugh classification A and B) as compared with nintedanib administration to male and female healthy subjects (a non-blinded, parallel group study of Phase I)’ was initiated in July 2014 and is ongoing. The study protocol (c02376885) is provided with these responses. | The sponsor’s response is satisfactory. |
| 8. It appears that the Australian PI for Vargatef and Ofev are currently in one document. The sponsor should clarify whether the two products will share the same PI. The draft PI document in its current form can be rather confusing as all the information including indication, dosage and administration, adverse reactions are presented together for the two products. | The sponsor wishes to clarify that in Australia, there is only one application for registration of nintedanib, covering both the NSCLC and IPF indications. Ofev is the preferred proposed trade name for the product, while Vargatef is a back-up trade name. Therefore, upon registration, there will only be one PI for the product. | The evaluator has noted the sponsor’s clarification. |
| 9. Liver enzyme elevation and hyper bilirubinaemia is an identified risk for both Vargatef and Ofev. The product label approved by the US FDA for Ofev contains the following detailed instruction on liver function monitoring: ‘*Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with Ofev, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications or interruption may be necessary for liver enzyme elevations.*’  In comparison, the proposed Australian PI provides a more general advice on the frequency of monitoring as follows: ‘*Hepatic transaminase and bilirubin levels should be investigated before the initiation of treatment with Ofev/Vargatef and periodically thereafter (for example at each patient visit) or as clinically indicated*.’  It is recommended that the Delegate considers this instruction in the context of improvement of the safety. | The recommendations for liver function monitoring in the proposed Australian PI are identical to the text approved by the EMA for Ofev (nintedanib in IPF).  Hepatic transaminase and bilirubin levels should be investigated before the initiation of treatment with nintedanib, as a baseline reference. The sponsor proposes that after start of treatment, liver enzymes and bilirubin should be measured periodically, for example at each patient visit, which could be at the patient’s IPF specialist or family physician, or as clinically indicated.  The sponsor anticipates that patients will be followed up by their physician more frequently during the first weeks/months after treatment with nintedanib, according to routine practice following initiation of a new treatment. As the risk of liver enzyme elevations is higher in these first months, the sponsor considers the proposed text in the ASA to be appropriate.  Compared to the more detailed recommendation requested by the FDA, the proposed flexible monitoring recommendations in the Australian PI allow the prescribing physicians to provide personalised liver monitoring frequency according to the patient’s medical history, condition, changes in concomitant therapy and so on.  When elevated levels of transaminases or bilirubin are detected, more frequent monitoring is indicated; the frequency again is based on the physician’s medical judgement, guided by the level of elevations and the action taken with the medication.  In conclusion, the sponsor believes that the proposed warnings on liver enzyme and bilirubin elevations with the actual monitoring frequency at the physician’s discretion are appropriate to ensure patient’s safety. | The evaluator has noted that the sponsor has updated the Australian PI to align with the relevant parts of the EU Summary of Product Characteristics (SmPC). In regard to the routine risk minimisation, the updated PI is considered acceptable. |

#### Summary of recommendations

It is considered that the sponsor’s response to the TGA request for information has adequately addressed all of the issues identified in the RMP evaluation report.

There are additional recommendations for the nonclinical evaluator.

##### Additional recommendations from the nonclinical evaluator

The sponsor has provided response to the following recommendations made by the nonclinical evaluator.

1. Reproductive and developmental toxicity;

Teratogenicity was observed in rats at exposures around 20 fold lower (IPF) or 30 fold lower (NSCLC) than the clinical exposure and in rabbits at exposures 4 to 5 (IPF and NSCLC) times the clinical exposure.

The summary paragraph of the RMP for NSCLC, which is in line with the TGA nonclinical evaluator’s assessment, is not included in the RMP for IPF.

1. Section ‘SIV.3.3 Pregnant or breastfeeding women’ in the RMP for IPF, does not include the following statement (which is included in the same section of the RMP for NSCLC): ‘*Women of childbearing potential should avoid becoming pregnant during treatment with Vargatef and use adequate contraceptive methods. Since the effect of nintedanib on the metabolism and efficacy of contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy.*’

*RMP evaluator’s comments:*

The RMP evaluator supports the recommendations made by the nonclinical evaluator. The proposed PI states that nintedanib is contraindicated during pregnancy. The PI also contains the advice that breastfeeding should be discontinued during treatment with nintedanib. Advice on contraceptive measures and pregnancy test prior to the commencement of treatment is also provided in the PI. The RMP evaluator considers these are adequate to mitigate the risks related to pregnancy and lactation. Nonetheless, the sponsor’s response to the nonclinical evaluator’s recommendations is expected to be evaluated by the nonclinical evaluator.

##### Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

##### Suggested wording for conditions of registration

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

Implement Vargatef EU-RMP version 2.1 dated 12 March 2015 (data lock point 15 February 2013) with Australian Specific Annex version 2.0 dated 26 March 2015; and Ofev EU-RMP Version 1.2 dated 30 December 2014 (data Lock Point 26 November 2013) with Australian Specific Annex version 2.0 dated 26 March 2015.

## VI. Overall conclusion and risk/benefit assessment

The submission was summarised by two units of the TGA, one for each of the indications. The Delegate constructed an overview and recommendations regarding the NSCLC indication whilst summary and recommendations regarding the IPF indication were prepared separately.

### Background

#### Non-small cell lung cancer

The two major types of lung cancer are small cell lung cancer (SCLC) and NSCLC; this comprises approximately 81% of lung cancers. Six percent of lung cancer originates from other cell types.

The WHO/IASLC histological classification of NSCLC is:

* Adenocarcinoma (38% of lung cancers; approximately 47% of NSCLC)
* Squamous cell carcinoma (20% of lung cancers; approximately 25% of NSCLC)
* Large cell carcinoma (5% of lung cancers; approximately 6% of NSCLC)
* Other (18% of lung cancers; approximately 22% of NSCLC)

These histological subtypes arise in different anatomical compartments, for example SQ NSCLC may often arise from the central airway compartment (so may be close to large vessels, etcetera). Some tumours have mixed histology.

About 15 to 30% of non-Asian and 30 to 60% of Asian patients with adenocarcinoma have a mutation in EGFR. ALK mutations are present in 2 to 7% of NSCLC patients in the US.

As well as histology, key influences on choice of initial therapy for advanced disease are:

* extent of disease (for example number and site of metastases)
* presence of symptoms related to a specific metastatic site
* presence of driver mutations (for example EGFR; ALK; ROS1) and
* the patient’s overall condition and co morbidities.

Influences on choice of subsequent therapy for advanced disease are similar. Another influence is choice of prior treatment (that is the need for a non cross resistant approach).

Treatment of advanced NSCLC aims to prolong survival and maintain quality of life, while minimising side effects of treatment. Almost all patients with advanced NSCLC eventually develop progressive disease.

Treatment of advanced NSCLC involves surgery, radiotherapy and/or chemotherapy. In local guidelines (Cancer Council Australia), each stage (I to IV) of NSCLC is divided into ‘operable’ and ‘non operable’. Surgery may not be possible due to comorbidity, poor lung function, tumour location or patient choice.

Table 17. Currently registered agents in Australia for treatment of NSCLC.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Active ingredient | Trade name | Sponsor | | Approved NSCLC indication |
| **Not restricted by line of therapy** | | | | |
| Pemetrexed disodium | Alimta | | Eli Lilly | Alimta in combination with cisplatin is indicated for initial treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.  Alimta as monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology after prior platinum based chemotherapy. |
| Docetaxel | various | | various | Indicated for the treatment of patients with locally advanced or metastatic non small cell lung cancer, including those who have failed platinum based chemotherapy. |
| Paclitaxel | various | | various | Treatment of non-small cell lung cancer (NSCLC) |
| Gemcitabine | various | | various | Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) |
| Erlotinib | Tarceva | | Roche | First line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer with activating EGFR mutations.  Maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not progressed on first line chemotherapy. Efficacy is influenced by tumour characteristics (see CLINICAL TRIALS).  Treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy. |
| Gefitinib | Iressa | | Astra Zeneca | Treatment of patients with locally advanced or metastatic Non-small Cell Lung Cancer (NSCLC) whose tumours express activating mutations of the EGFR tyrosine kinase |
| Afatinib | Giotrif | | BI | GIOTRIF is indicated as monotherapy for the treatment of patients with advanced or metastatic non squamous non-small cell carcinoma of the lung, either as first line therapy or after failure of cytotoxic chemotherapy. Tumours must have Epidermal Growth Factor Receptor (EGFR) exon 19 deletions or L858R substitution mutations. |
| Crizotinib | Xalkori | | Pfizer | XALKORI is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK) positive advanced non small cell lung cancer (NSCLC). |
| **First line** | | | | |
| Vinorelbine | various | various | | First line treatment for advanced non-small cell lung cancer, as a single agent or in combination |
| Etoposide | various | various | | No formal indication in NSCLC (but mentioned in NSW Cancer Institute’s EviQ) |
| Cisplatin | various | various | | No formal indication in NSCLC (but mentioned in EviQ and referred to in other products’ indications) |
| Carboplatin | various | various | | No formal indication in NSCLC (but mentioned in EviQ and referred to in other products’ indications) |
| Bevacizumab | Avastin | Roche | | Avastin (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first line treatment of patients with unresectable advanced, metastatic or recurrent, non squamous, non-small cell lung cancer. |

#### Role of docetaxel in NSCLC

The following sections present guidance from various sources with regard to the role of docetaxel in NSCLC.

###### EviQ

Metastatic NSCLC chemotherapy protocols on EviQ[[26]](#footnote-27) include a docetaxel three weekly and a docetaxel weekly regimen. The three weekly regimen recommends a 75 mg/m2 dose, given IV on Day 1 of each 3 week cycle, for 4 cycles unless otherwise indicated. There is a note that ‘*if treatment is to be used as second line therapy the low response rate and short duration of remission should be considered and discussed with the patient’*. The weekly regimen (30 mg/m2 on Days 1, 8 and 15 of a 28 day cycle, for 4 cycles unless otherwise indicated) includes the same note. Several studies mentioned in EviQ suggest similar efficacy but lower toxicity with weekly as opposed to three weekly docetaxel.

###### NCCN

Version 5.2015 of the US NCCN[[27]](#footnote-28) guidelines for NSCLC states that ‘*in patients who have experienced disease progression either during or after first line therapy, single agent docetaxel, pemetrexed or erlotinib are established second line agents*’ (and also that pemetrexed is considered equivalent to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma).

###### Clinical guidelines

‘Clinical practice guidelines for the treatment of lung cancer’[[28]](#footnote-29) discuss optimal second line therapy in patients with Stage IV inoperable NSCLC. The guidelines indicate that in unselected patients previously treated for advanced NSCLC, chemotherapy with docetaxel or pemetrexed is appropriate, though pemetrexed may have advantages in non-squamous NSCLC. An alternative is erlotinib. The guideline also states that in patients with Stage IV inoperable NSCLC and known activating EGFR gene mutations, an EGFR TKI should be used.

###### Up to date

In the discussion ‘*Advanced non-small cell lung cancer: subsequent therapies for previously treated patients*’[[29]](#footnote-30), the approach to subsequent treatment depends on whether initial treatment is chemotherapy or targeted therapy:

* After combination chemotherapy, and if no driver mutation is present (or if mutation status is unknown), in patients with NSCLC, nivolumab is recommended as the initial treatment, and chemotherapy with a non-cross resistant agent is reserved for those who have progressed on immunotherapy. However, the inference is that in the absence of nivolumab (for example if immunotherapy is contraindicated), docetaxel is an appropriate single agent chemotherapy. Pemetrexed is restricted to patients with non-squamous histology. It is also noted that 75 mg/m2 is an appropriate once every three weeks (Q3W) dose for docetaxel in this setting, and that weekly 33.3 mg/m2 dosing may minimise haematological toxicity, but exacerbate other toxicities (for example tear duct stenosis).
* After combination chemotherapy, and if a driver mutation is present, a targeted inhibitor is usually used. Single agent chemotherapy can be used when progression occurs after treatment with the targeted therapy.
* After targeted therapy, combination chemotherapy followed by single agent maintenance therapy is recommended, followed by single agent chemotherapy upon further disease progression.

###### Docetaxel PI

The docetaxel (Taxotere) PI includes the following indication in NSCLC:

*Taxotere is indicated for the treatment of patients with locally advanced or metastatic NSCLC, including those who have failed platinum based chemotherapy.*

The recommended dosage in NSCLC is ‘75 to 100 mg/m2 administered as a one hour infusion every three weeks. A dose of 100 mg/m2 has been shown to result in a moderate increase in response rates compared with 75 mg/m2 but is associated with greater toxicity’. In the key study febrile neutropenia was a major toxicity observed at a higher frequency at 100 mg/m2.[[30]](#footnote-31)

###### Literature

Many papers show use of docetaxel in this setting, for example:

Garassino et al (‘TAILOR’; NSCLC with wild-type EGFR; 75 mg/m2 docetaxel; addition of erlotinib resulted in no improvement in OS, with an hazard ratio (HR) of 0.73 favouring docetaxel)[[31]](#footnote-32)

Garon et al (‘REVEL’; all NSCLC; 75 mg/m2 docetaxel, although a protocol amendment stipulated that new patients enrolled in east Asia should receive 60 mg/m2; addition of ramucirumab resulted in an improvement in OS, with a HR of 0.86).[[32]](#footnote-33)

These studies support the use of a 75 mg/m2 dose of docetaxel as an acceptable comparator in this setting.

### Quality

The proposed product is a liquid suspension of nintedanib esilate, enclosed in a soft gelatin capsule. The composition of this liquid suspension has remained unchanged during clinical development.

There were no objections to registration based on chemistry; manufacturing controls and biopharmaceutics.

### Nonclinical

There were no objections on nonclinical grounds to the registration of nintedanib for the proposed indications, assuming adequate monitoring/management during clinical use.

### Clinical

### Overview of data - NSCLC

There was one pivotal study in NSCLC (Study 1199.0013), and there were two principal supportive studies (1199.0014 and 1199.0010).

##### Study 1199.0013

This was a large, randomised study of nintedanib and docetaxel versus placebo and docetaxel, in advanced NSCLC patients (including patients with adenocarcinoma or squamous histologies) who had failed first line therapy. The study has been published.[[33]](#footnote-34)

##### Study 1199.0014

This was a large, randomised study of nintedanib and pemetrexed versus placebo and pemetrexed, in patients with advanced non squamous NSCLC that is mainly in patients with adenocarcinomas, who had failed first line therapy. The study was conspicuous for failing a pre-planned test of futility, so that recruitment was stopped early.

##### Study 1199.0010

This was a small, Phase II study that compared different doses of nintedanib (as monotherapy) in advanced NSCLC.

##### Other studies

There was a range of clinical pharmacology studies, including three population PK analyses.

Additional studies, considered not relevant by the clinical evaluator, (see Table 1, Attachment 2). Of note, several of these studies were in patients with NSCLC, but in these studies, nintedanib was used in combination with chemotherapies other than docetaxel.

#### Pharmacokinetics (PK)

PK characteristics of nintedanib were adequately characterised.

##### Pharmacokinetics in healthy subjects

Of note from studies in healthy subjects:

* Absolute bioavailability is low (4.7%); this was attributed to extensive first pass metabolism and/or a low absorption due to P-gp-mediated efflux in the gut.
* There is extensive tissue distribution (for example volume of distribution is 1,050 L after a 6 mg IV dose).
* Nintedanib is metabolised by esterases to the metabolite BIBF 1202, which is then glucuronidated by UGT enzymes; neither metabolite is thought to contribute to clinical effects. The nonclinical evaluation report noted a lack of studies of potential pharmacological activity of the BIBF 1202 glucuronide; the sponsor has supplied top line information to the effect that the BIBF 1202 glucuronide metabolite does not appreciably inhibit VEGFR 1-3, FGFR 1-4 and PDGFR α and β.

**Comment:** The sponsor is requested to supply the cited data.

* Clearance of nintedanib is predominantly non renal, for example after 6 mg IV nintedanib, only 1.4% of the dose is excreted unchanged in urine over 48 hours.
* After administration of oral radiolabelled nintedanib, little radiolabel is excreted in urine, and 93.4% of radioactivity is excreted in faeces.
* Half-life (estimated using a 6 mg IV dose) is 18 hours; half-life (estimated with oral dosing in healthy volunteers) is 12 to 23 hours.

The nonclinical evaluation also noted that there was ‘limited’ penetration of the blood brain barrier, elsewhere described as negligible. Modulation of P-gp (for example inhibition or induction with other drugs) might also influence exposure in the CNS.

##### Pharmacokinetics in the target population

Of note from studies in the target population:

* Tmax is 2 to 4 hrs.
* Dose proportionality was not seen across studies in advanced cancer patients, but the population PK analysis found no major deviation from linear PK
* Based on trough concentrations, steady state is reached by Day 7 of dosing
* Homozygosity for UGT1A1\*28 may lead to a modest increase in exposure

There were no completed specific studies of nintedanib PK in hepatic impairment.

**Evaluator’s comment:**

The sponsor should undertake to provide completed clinical study reports (CSRs) of studies examining the effects of hepatic impairment in PK of nintedanib as the CSRs become available.

There were no specific studies in renal impairment. Very few subjects with severe renal impairment were considered in population PK analyses. However, given the absence of any influence on PK of creatinine clearance in the main population PK analysis (which did take into account subjects with mild and moderate renal impairment) and given the minor contribution of renal clearance to overall clearance, the sponsor’s view that there need be no recommendation against use in severe renal impairment is reasonable.

In the main population PK analysis, subjects from China, Taiwan and India had a 33% increase in systemic exposure.

The clinical evaluator states ‘*the main population PK analysis indicated that there were no differences in PK between the NSCLC and IPF populations’*.

##### Interactions with other medicines

Key information about interactions with other medicines follows:

* Nintedanib is a substrate for P-glycoprotein, and human studies show that use with the P-gp inducer rifampicin results in a 50% decrease in bioavailability of nintedanib, while use with the P-gp inhibitor ketoconazole results in a 60 to 70% increase in bioavailability.
* In vitro data suggested nintedanib does not inhibit P-gp at relevant concentrations
* In patients with prostate cancer, nintedanib did not influence docetaxel PK
* Nintedanib bioavailability may be reduced if co administered with pH raising agents such as proton pump inhibitors (submitted data are in conflict on this point).

The nonclinical evaluation report also noted that nintedanib inhibited UGT, which may influence the PK of drugs predominantly metabolised by glucuronidation. Report U06‑1744 (in vitro data) concluded that clinically relevant interactions are likely to be rare, because inhibition was seen at a high concentration and also because few drugs depend for their clearance solely on glucuronidation; effects were only tested for UGT1A1 and 2B7. However, the nonclinical evaluator considered it would be useful to understand whether the metabolite BIBF 1202 glucuronide affects UGT enzymes. The sponsor has provided clarification about this issue, proposing to supply data post registration.

**Evaluator’s comment:**

Could the sponsor clarify whether there may be inhibition of other relevant UGT isoforms, by the parent drug or its metabolites?

#### Pharmacodynamics

Several studies assessed changes in tumour vasculature using magnetic resonance imaging (MRI) techniques, or effects on plasma biomarkers, but none is influential in assessing the product’s efficacy/ safety.

#### Efficacy in lung cancer

The clinical evaluator considers the evidence for efficacy is sufficient to support the proposed use in lung cancer.

#### Dosage selection

Dosage selection for the pivotal NSCLC trial is considered in the review of Phase I Study 1199.0004. The maximum tolerated dose was considered to be 200 mg BD. The sponsor reached the same conclusion about the maximum tolerated dose after review of Phase I Studies 1199.001, 1199.002 and 1199.003. Phase II Study 1199.0010 of nintedanib monotherapy in NSCLC found no differences in efficacy between 150 mg BD and 250 mg BD dosing.

**Evaluator’s comment:**

Could the sponsor clarify why 150 mg BD dosing was not tested in pivotal studies (of NSCLC)?

##### Pivotal Study 1199.0013 (‘LUME-Lung 1’)

The pivotal Study 1199.0013 (‘LUME-Lung 1’) is described in Section 7.1.1.1 of Attachment 2. It was a double blind study initiated in 2008 across 27 countries (mainly in Europe). It randomised n = 1,314 adults who had failed first line chemotherapy treatment of stage IIIB/IV or recurrent NSCLC into one of two arms, receiving 21 day cycles of either:

* Docetaxel (75 mg/m2) IV on Day 1, then nintedanib 200 mg BD on Days 2 to 21; or
* Docetaxel (75 mg/m2) IV on Day 1, then placebo BD on Days 2 to 21.

Randomisation was stratified by Eastern Cooperative Oncology Group (ECOG) performance score (0/1), squamous/non squamous histology, presence/absence of brain metastases and previous bevacizumab therapy (yes/no).

Treatment was continued until progression or lack of tolerability. Subjects who had to discontinue one component could potentially continue on the other component, in both arms. There was no cross over from placebo after progression.

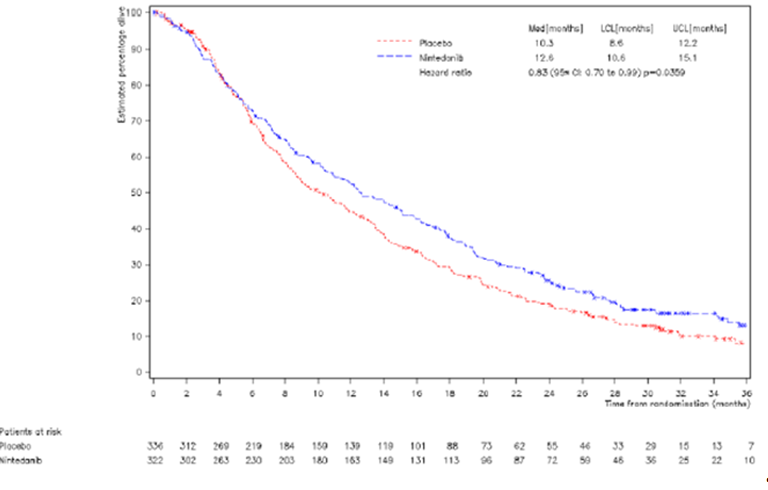
Some 655 subjects were randomised into the nintedanib + docetaxel arm, and 659 into the placebo + docetaxel arm. Baseline characteristics are shown in Table 14, Attachment 2. The arms were well balanced with regard to important prognostic factors such as stage and age. In total, 50% of subjects had adenocarcinoma, 42% had squamous cell carcinoma, 3% had large cell carcinoma and 5% had other classifications.

The primary efficacy outcome was PFS by blinded central review. The primary analysis of PFS was in November 2010, at which point only 1,134 subjects had been randomised (but also at which point, 714 PFS events had occurred). Nintedanib was associated with a 21% reduction in risk of progression or death (HR 0.79, 95% CI 0.68 to 0.92). Median PFS was prolonged from 2.7 to 3.4 months, which is approximately a 3 week difference.

A follow up PFS analysis (at the time of the final OS analysis, February 2013) found a 15% reduction in risk of progression or death (HR 0.85, 95% CI 0.75 to 0.96). Median PFS was prolonged from 2.7 to 3.5 months. These outcomes were across all studied subjects. The sponsor also presented analyses of primary PFS outcomes in subjects with squamous versus non squamous histology; HRs were 0.77 (95% CI 0.62 to 0.96) and 0.81 (95% CI 0.66 to 0.99) respectively. The primary HR in adenocarcinoma was 0.77 (95% CI 0.62 to 0.96), according to the sponsor’s clinical overview, and the follow up HR in adenocarcinoma was 0.84 (95% CI 0.71 to 1.00).

The pre specified OS analysis approach was modified. An OS benefit was found in subjects with adenocarcinoma histology. The HR was 0.83 (95% CI 0.70 to 0.99), with an improvement in median OS from 10.3 to 12.6 months. The Kaplan-Meier curve is shown in Figure 4. The evaluator considered the average 2.3 month prolongation of life clinically significant.

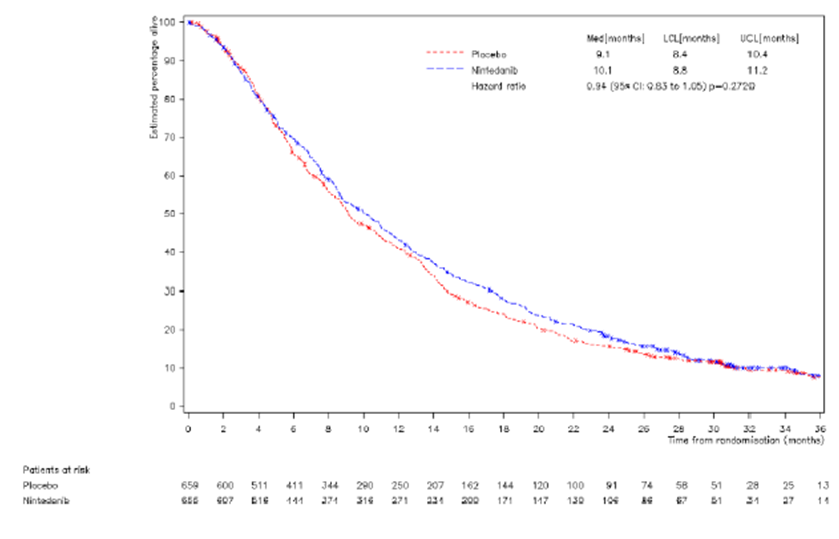
Figure 4. Study 1199.0013: Overall survival (adenocarcinoma patients).



Appraisal of Study 1199.0013 by SwissMedic, as shared with the TGA by the sponsor, suggested the pre specified approach to OS analysis was modified because of findings from the primary PFS analysis within Study 1199.0013. The CSR for Study 1199.013’s final OS report states, ‘*the exploratory analyses performed for trials 1199.14 and 1199.13 led to the identification of a subgroup of patients that seemed to obtain a clinical benefit from study treatment with nintedanib in combination with chemotherapy’*. It appears that the pre specified approach to analysis of OS in Study 1199.0013 was modified at least in part because of exploratory analyses conducted on unblinded data in the same study. These exploratory analyses were apparently recommended by the Data Monitoring Committee, as a way of identifying a subgroup that would respond to nintedanib/benefit from treatment.

There was no clear survival benefit from adding nintedanib in analysis of all subjects; the HR was 0.94 but the 95% CI was 0.83 to 1.05. The Kaplan-Meier curve is in Figure 5. For squamous histology, the HR was 1.01 (95% CI 0.85 to 1.21).

Figure 5. Study 1199.0013 – Overall survival (all patients).



In the final OS analysis for Study 1199.0013, subsequent use of anti-cancer drugs is fairly balanced, but there is some imbalance in use of investigational anti-cancer drugs (1.2% for placebo arm, 4.7% for nintedanib arm, in the adenocarcinoma subset).

**Evaluator’s comment**:

The sponsor should clarify whether anti-PD-1 antibodies were used, as these have shown efficacy in second line NSCLC.[[34]](#footnote-35)

Enrolment in studies of anti-PD-1 drugs may not have been common in the period when Study 1199.0013 patients were being followed up for use of subsequent anti-cancer agents.

Other endpoints are discussed in Attachment 2. In broad terms there was no improvement in the rate of objective response with addition of nintedanib; there was a modest improvement in disease control rate (41% with placebo to 54% for nintedanib, in all patients); and there was less time until deterioration of diarrhoea as measured in a quality of life questionnaire (HR 1.9, 95% CI 1.67 to 2.26). Despite the later observation, a decrease in global quality of life with nintedanib was not apparent.

##### Non-pivotal Study 1199.0014 (‘LUME-Lung 2’)

This study is reviewed in Attachment 2 Section 7.1.2.1. It was a Phase III, randomised, double blind study of patients with stage IIIB or IV or recurrent NSCLC with non squamous histology, after failure of 1st line chemotherapy. It started in 2008. Subjects received pemetrexed and nintedanib, or pemetrexed and placebo. (The sponsor is not seeking approval for use of nintedanib in combination with pemetrexed.)

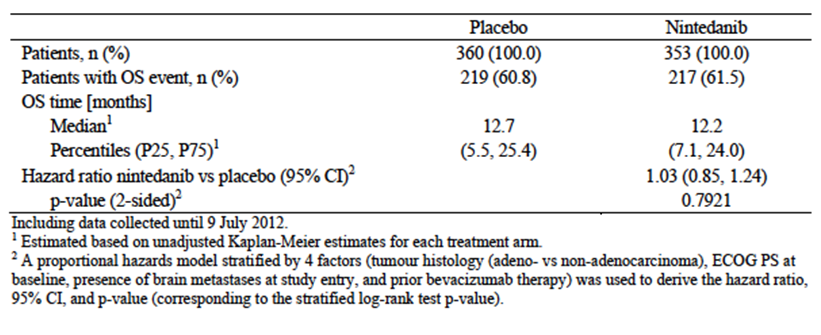
A pre-planned futility analysis based on investigator assessed PFS was conducted after 341 PFS events. The data monitoring committee recommended the trial stop because it was unlikely to meet its efficacy objective. (A retrospective review of data at the time corresponding to the data monitoring committee snapshot, 14 March 2011, showed an HR for investigator assessed PFS of 0.92 (95% CI 0.74 to 1.14); and toxicity was not a concern). Recruitment was stopped in June 2011. The sponsor somewhat dissociated itself from this decision by the data monitoring committee, for example from the CSR synopsis:

*‘The retrospective analyses revealed that the secondary endpoint PFS by investigator assessment, which was used for the futility analysis, had a less favourable outcome than the analysis of the primary endpoint that is PFS by central independent review. Also, the time point of the pre-defined futility analysis seemed to be the one with the least favourable outcome. Nevertheless, the hazard ratio of PFS by investigator assessment was < 1 and the lower boundary of the 95% CI was as low as 0.74 at the time of the pre-defined futility analysis. Furthermore, no safety issues with nintedanib were observed. These results, together with warnings from literature about the dangers of too aggressive stopping rules and wrong interpretations of negative interim results based on immature data, should have been considered, possibly leading to the decision to continue trial 1199.14 as planned.’*

Some 94% of randomised subjects had adenocarcinoma histology. A small number of subjects had non adenocarcinoma histology; whether these subjects had squamous histology is not clear from the CSR’s presentation of baseline disease characteristics, but it does not seem likely many subjects with squamous histology would have been enrolled, given the pemetrexed backbone.

Addition of nintedanib was associated with a statistically significant reduction in risk of progression or death (HR 0.83; 95% CI 0.70 to 0.99). Median PFS was increased from 3.6 to 4.4 months. There was no observed difference in OS (Table 18, below). In the presented sub group analysis, for the predominant adenocarcinoma subgroup, the HR was 0.85 (95% CI 0.69 to 1.04) in favour of nintedanib, with median PFS 3.6 months in the placebo arm, 4.2 months in the nintedanib arm.

Table 18. Study 1199.0014 Analysis of overall survival.



#### Safety in lung cancer (NSCLC indication)

A total of 1,880 cancer subjects were exposed to nintedanib, although average duration of exposure was short (median 3.4 months in Study 1199.0013) and only 146 subjects received nintedanib for > 12 months.

A conspicuous safety finding in the adenocarcinoma subset of Study 1199.0013 was the elevated frequency of fatal SAEs in the nintedanib group (17.5%) versus the placebo group (9.6%). Overall survival outcomes, mentioned above, put this finding into context. The imbalance is characterised in Table 19 below and Table 36 of Attachment 2. Respiratory failure and sepsis were key drivers. Other SAEs were broadly balanced across arms (Table 11 above). A higher rate of fatal SAEs was not seen in Study 1199.0014, and there was no specific imbalance (within 1199.0014) across arms in deaths due to respiratory failure (Table 37 Attachment 2). The clinical evaluator notes that in Study 1199.0013, of 7 cases of fatal sepsis in the nintedanib arm, there was an association with neutropenia in 4 cases (and no data in the other 3 cases). There was only 1 case in the placebo arm, suggesting at least a possible synergy with docetaxel in this regard. Febrile neutropenia may be more common with addition of nintedanib (Table 20 below).

Table 19. Study 1199.0013 (All patients) AEs leading to death.

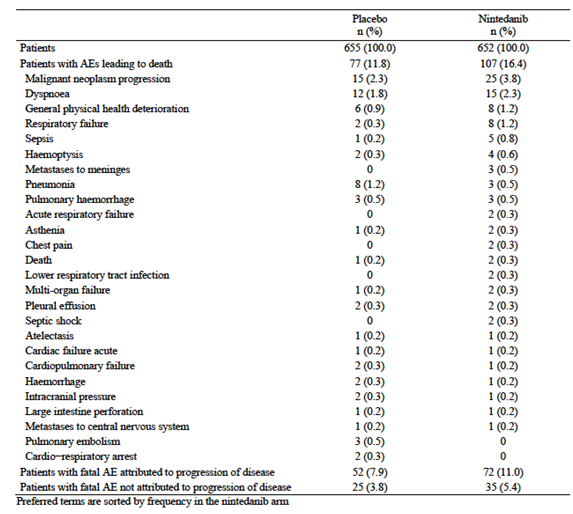
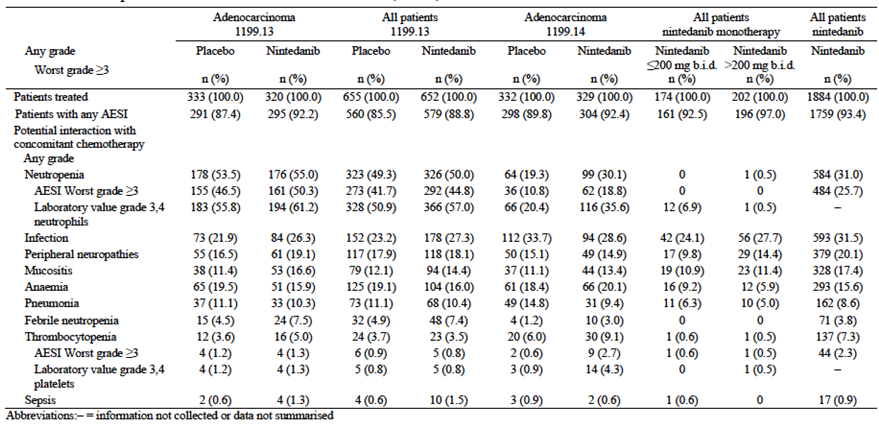


Table 20. NSCLC studies – AEs of special interest (potential interaction with chemotherapy). Summary of adverse events of special interest as potential interaction with concomitant chemotherapy in Phase III trials 1199.13 and 1199.14 (SAF-1), in nintedanib Phase I/II monotherapy trials (SAF-2) and in patients with cancer treated with nintedanib (SAF-3)-TS.



Common AEs with frequencies differing in the nintedanib and placebo arms in Study 1199.0013 (adenocarcinoma group) were, from Table 33 Attachment 2, diarrhoea (43.4% versus 24.6%), ALT increased (37.8% versus 9.3%), AST increased (30.3% versus 7.2%), nausea (28.4% versus 17.7%), and to a lesser extent anorexia, vomiting and stomatitis. The pattern varied slightly in Study 1199.0014 where pemetrexed was the backbone, but LFT derangement and diarrhoea were the most prominent toxicities linked to nintedanib. A similar pattern emerged from review of drug related AEs (Table 35 Attachment 2 and Tables 21 and 22 below). The clinical evaluator notes serious gastrointestinal and hepatic AEs were not prominent in nintedanib arms. Atrial fibrillation was reported as an SAE within Study 1199.0013’s adenocarcinoma subset in 4 nintedanib but 0 placebo subjects.

Table 21. Study 1199.0013 (All patients) – Drug related AEs.

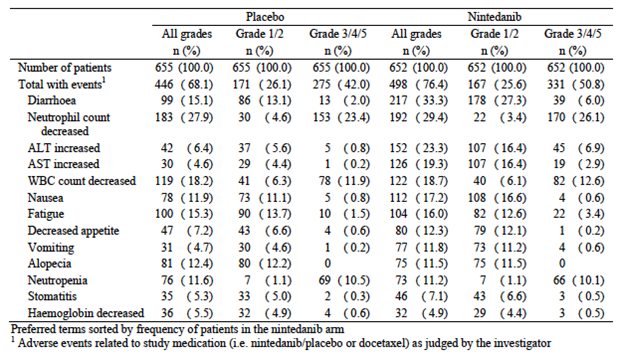
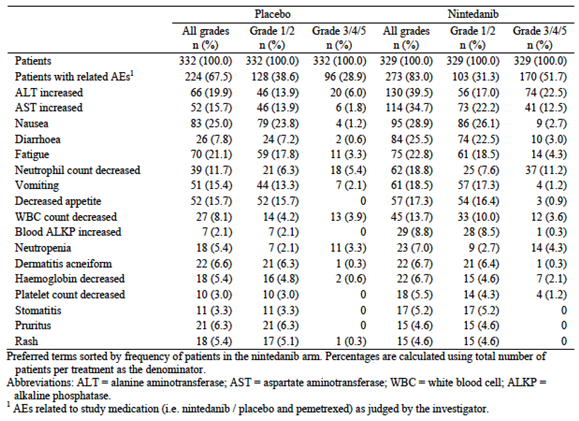


Table 22. Study 1199.0014 (Adenocarcinoma patients) – Drug-related AEs.



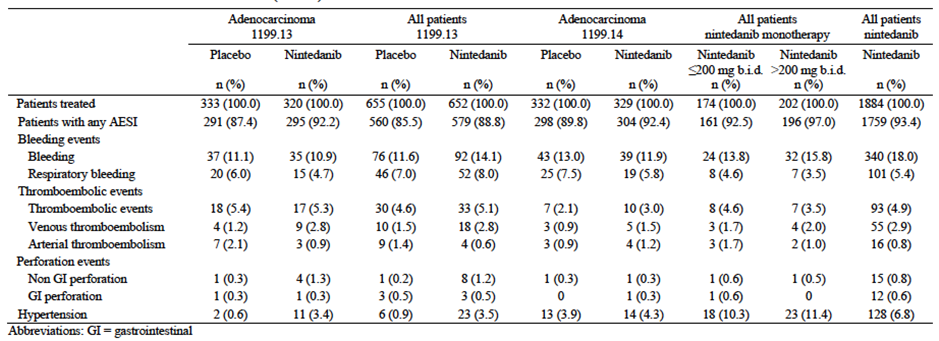
**Evaluator’s comment:**

The sponsor is invited to comment on likely mechanisms resulting in diarrhoea, in the light of rat data indicating dose dependent inhibition of gastrointestinal tract motility yet symptomatic use of loperamide in clinical trials. Is there objective evidence that anti motility agents are beneficial in the treatment of nintedanib induced gastrointestinal toxicity?

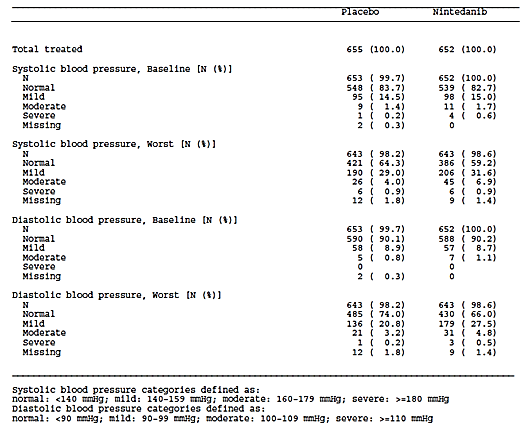
Consistent with a high frequency of transaminitis observed with nintedanib, there was an imbalance in AEs aligned with hepatic failure: in Study 1199.0013, across all subjects, 1 placebo (0.2%) versus 8 nintedanib (1.2%) subjects had ‘hepatic failure’, and in Study 1199.0014, the imbalance was as pronounced: 2 placebo (0.6%) versus 8 nintedanib (2.4%) subjects. Actual preferred terms encompassed a range of AEs, not all incontrovertibly reflecting liver injury (for example ascites). However, the imbalance consistent across two studies, in the context of a clear impact on transaminases, is a strong signal that nintedanib may cause liver injury.

Frequencies of AEs considered potential class effects of VEGFR inhibitors are set out in Table 23 and there was no consistent signal of a large imbalance versus placebo, though there may be a moderate signal for venous thromboembolism. Whether this is via VEGFR inhibition directly is not clear (for example diarrhoea causing dehydration might also contribute to risk of VTE). There was a signal in Study 1199.0013 that in some patients, hypertension may occur on nintedanib (Table 24). Further, the clinical evaluator reported that in studies of patients with idiopathic pulmonary fibrosis, nintedanib was linked to elevated risk of arterial thromboembolic events, bleeding and gastrointestinal perforation. Many exclusion criteria in the Phase III NSCLC studies tended to exclude patients at risk of VEGFR inhibitor class effects (‘history of major thrombotic or clinically relevant major bleeding event in the past 6 months’ and so on).

Table 23. NSCLC Studies AEs of special interest (VEGFR inhibitor class effects). Summary of adverse events of special interest as potential class effects of VEGFR inhibitors in Phase III trials 1199.0013 and 1199.0014 (SAF-1), in nintedanib Phase I/II monotherapy trials (SAF-2), and in patients with cancer treated with nintedanib(SAF-3) –TS.



**Table 24. Study 1199.0013 (All patients) – Blood pressure changes.**



Interstitial lung disease was more common in nintedanib patients than placebo patients in Study 1199.0013 (docetaxel backbone; docetaxel is linked to drug induced ILD), but the opposite pattern was noted in Study 1199.0014 (pemetrexed has also been linked to ILD). Drug induced ILD and idiopathic pulmonary fibrosis are distinct entities. On the other hand, in vivo efficacy of nintedanib in nonclinical studies used bleomycin induced lung fibrosis in mice and rats, and silica induced lung fibrosis in mice.

### Overview of data for IPF

#### Background

Ofev/Vargatef is also indicated for the treatment of IPF and to slow disease progression. It is noted that the trade name, Ofev relates to the IPF indication (in overseas jurisdictions). At present, there are no registered medications for the treatment of IPF.

According to the sponsor, preclinical data suggest a potential role of FGF and PDGF signalling in the pathogenesis of IPF. Hence, the clinical rationale is based on nintedanib’s ability to inhibit the receptors for these factors.

#### Nonclinical

This section only deals with relevant information to register IPF.

The nonclinical evaluator mentions that, ‘*in mouse and rat animal models of pulmonary fibrosis, nintedanib administration for 30 days was efficacious and tolerated. Nintedanib was more efficacious as a preventer than as a therapeutic against pulmonary fibrosis’*.

Plasma nintedanib concentrations at effective doses in the mouse and rat pharmacology studies for both indications were similar to those in patients.

Safety pharmacology studies showed some sluggishness in gut motility. There were no significant effects seen in relation to cardiovascular, respiratory, renal, gastrointestinal and central nervous systems.

Approval from a nonclinical point of view is recommended.

#### Clinical

##### Pharmacokinetics

The clinical evaluator mentions that ‘*the main population PK analysis indicated that there were no differences in PK between the NSCLC and IPF populations’*.

Overall, the clinical evaluator states that the PK data in the submission are considered adequate to support registration. It was the opinion of the evaluator that further information on the effect of hepatic impairment should be provided.

##### Pharmacodynamics

The sponsor states that nintedanib ‘*is believed to exert its effects in IPF by blocking signalling pathways of PDGFR α and β, FGFR 1-3, and VEGFR 1-3 receptors involved in lung fibrosis. It binds competitively to the ATP binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation, migration and transformation of fibroblasts representing essential mechanisms of the IPF pathology’*.

This is not confirmed with pharmacodynamic studies.

##### Dose ranging studies

There was one dose finding study, 1199.0030. This was a randomised, double blind, placebo controlled Phase II study using 4 doses of active versus placebo, for 52 weeks.

The study enrolled subjects with IPF diagnosed according to ATS/ERS criteria. The dose of 150 mg BD was found to have beneficial effects.

##### Efficacy

The clinical evaluator discusses 2 pivotal studies (1199.0032 and 1199.0034) (see Attachment 2 Section 7.2.2). These studies were Phase III, randomised, double blind placebo controlled studies. They have been considered together as they were similar in design. These studies were 52 weeks in duration comparing 150 mg BD nintedanib versus placebo.

Inclusion and exclusion criteria are detailed in Attachment 2, Tables 21 and 22. The diagnosis of IPF was in line with the criteria set out in a widely accepted international consensus guideline on the diagnosis and management of IPF. Diagnosis was confirmed by central reading of chest high resolution X-ray computed tomography (CT) scan (HRCT) and surgical lung biopsy (if available). The study did not include subjects with more advance disease (for example FVC < 50%).

###### Efficacy variables

The efficacy variables are discussed in Section 7.2.2.1.4 of Attachment 2.

The primary efficacy endpoint was the annual rate of decline in FVC (expressed in mL over 52 weeks).

The key secondary efficacy outcomes were:

* Change from baseline in the Saint George’s Respiratory Questionnaire (SGRQ) total score at 52 weeks (expressed in points)
* Time to first acute IPF exacerbation (as assessed by the investigator) over 52 weeks.

Sample size calculations were based on the expected difference in FVC over 52 weeks between the nintedanib and placebo groups was 100 mL. Statistical testing is discussed. It is noted that the primary endpoint (annual rate of decline in FVC) was analysed using a random coefficient regression model.

###### Results

Across the two trials, 1,066 subjects were randomised, and 1,061 were treated, 638 with nintedanib and 423 with placebo. Approximately 84% of subjects completed the study.

Baseline demographics were provided (see Tables 26 and 27, Attachment 2). In the pooled population 8.9% of subjects in the nintedanib arm and 8.3% of subjects in the placebo arm were using oxygen at baseline. Systemic corticosteroid use was also comparable (21.3% versus 21.0%).

The clinical evaluator also mentions that, ‘*there were no significant imbalances between treatment arms with respect to baseline characteristics. The male to female ratio was high (4:1) in both trials. Consistent with the known clinical features of IPF, mean age in the pooled population was 66.8 years, and the majority of patients were current or ex smokers*’.

Primary efficacy analysis

They are included in Table 28 and Figure 9 of Attachment 2.

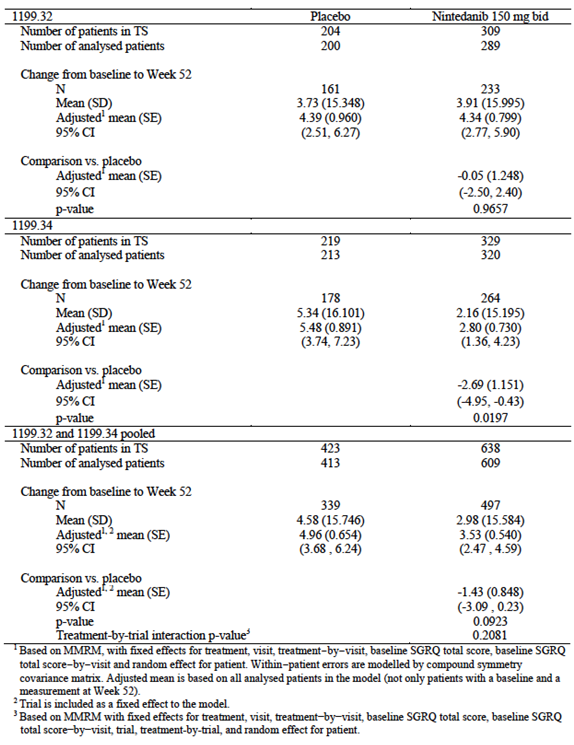
In both studies and in the pooled analysis, nintedanib treatment was associated with a significantly lower annual rate of decline in FVC.

* In Study 1199.0032 the adjusted rate of change was ‑239.91 mL/year with placebo and ‑114.65 mL/year with nintedanib (difference 125.26 mL/year; p < 0.0001).
* In Study 1199.0034 the adjusted rate of change was ‑207.32 mL/year with placebo and ‑113.59 mL/year with nintedanib (difference 93.73 mL/year; p = 0.0002).

Change from baseline in SGRQ total score at 52 weeks

Change from baseline in SGRQ total score at 52 weeks (Table 25 below).

Table 25. Studies 1199.0032 and 1199.0034 – Change in SGRQ total score at 52 weeks.



A statistically significant benefit was observed with nintedanib treatment in Study 1199.0034, and no significant difference between treatments in Study 1199.0032. When the data were pooled no significant difference between treatments was observed.

The clinical evaluator states that, ‘*in Study 1199.0034 the SGRQ total score increased in both groups, indicating deterioration in quality of life (Qo)L. The increase was less marked in the nintedanib group (mean change 2.16 versus 5.34 points) and the difference was statistically significant. However the adjusted mean difference was only 2.69 points. The minimum clinically important difference on the SGRQ is 4 points. Hence the effect of nintedanib on SGRQ total score is unlikely to be clinically significant’*.

Time to first acute IPF exacerbation

Time to first acute IPF exacerbation also revealed conflicting results. Study 1199.0034 demonstrated a significant benefit with nintedanib, and Study 1199.0032 showed no significant difference. When results of the two studies were pooled there was a lower incidence of exacerbations with nintedanib (4.9% versus 7.6%) but the difference was not statistically significant (p = 0.0823).

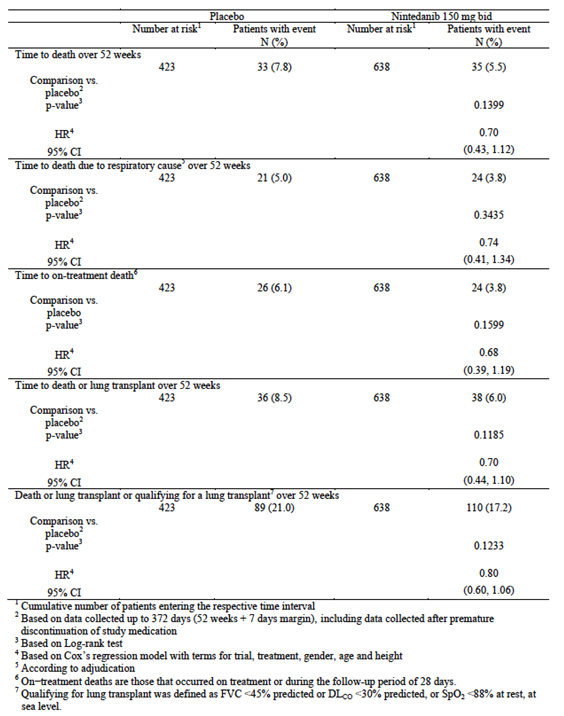
Results of other secondary efficacy endpoints

In relation to these, the evaluator concludes that there was no clinically significant effect on quality of life measures or respiratory symptoms.

###### Survival analyses

There were no significant differences on any of the survival endpoints either in the analyses of pooled data, (see Table 26) or the individual studies. The evaluator mentions that ‘*survival data were not mature with only 6.4% of subjects having died. Subjects are not being followed up long term for survival*’.

Table 26. Studies 1199.0032 and 1199.0034 – Survival endpoints.



###### Overall efficacy conclusion

The clinical evaluator concludes that the two well conducted Phase III pivotal studies showed statistically significant efficacy of nintedanib over placebo in relation to the primary efficacy endpoint, FVC. In relation to the secondary endpoints such as acute exacerbation, quality of life measure, dyspnoea and cough, there was no convincing evidence that nintedanib was favourable over placebo.

The evaluator discusses the merits (or lack thereof) of using FVC as the primary efficacy endpoint. This has been a subject of debate as it is felt that hard endpoints such as mortality should be used in these studies. Despite the lack of such data, FDA and EMA have approved pirfenidone and nintedanib based on studies that demonstrated a benefit on FVC.

The clinical evaluator mentions that, ‘*the pivotal studies in this submission demonstrated that nintedanib significantly reduces the proportion of patients experiencing a 5% or 10% decline in FVC. A decline of 5 to 10% in FVC has been associated with an increased risk of death in the following 12 months’*.

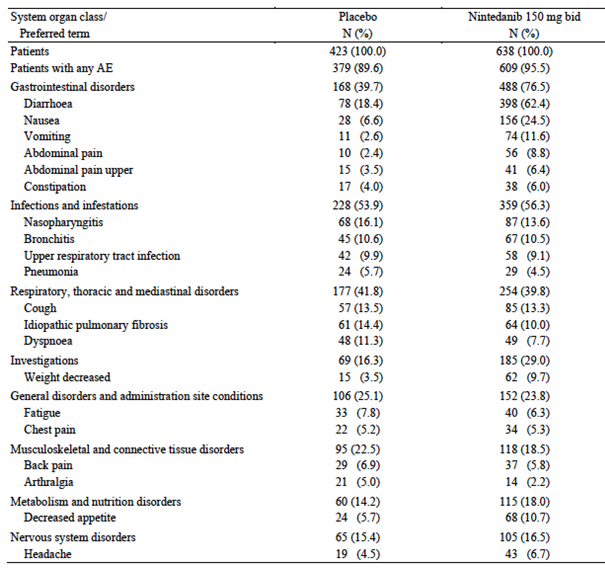
The studies did not include patients with more severe disease. It is recommended that the indication be limited to ‘*mild to moderate IPF*’ with explanatory text in the Clinical Trials section of the PI.

##### Safety - IPF

For detail see Attachment 2 Section 8.2. Some 423 patients were enrolled in the placebo and 638 patients in the nintedanib 150 mg BD group in the Phase III studies.

In the pivotal studies nintedanib treatment was associated with a small increase in the overall incidence of AEs (95.5% versus 89.6%). Common AEs (incidence > 5%) are shown in Table 27. Gastrointestinal toxicity (diarrhoea, nausea and vomiting, abdominal pain, decreased appetite) was far more common with nintedanib (76.5%) than with placebo (39.7%). Abnormal investigations were also more common with nintedanib (29 versus 16%). The most common event under this heading was decrease in weight.

Table 27. Studies 1199.0032 and 1199.0034 – Common AEs (incidence > 5%).



Drug related AEs were significantly more common with nintedanib than with placebo (71.3% versus 28.4%). Common drug related AEs (incidence > 2%) are shown in Attachment 2 Table 44. Gastrointestinal toxicity (62.4% versus 17.7%) and hepatotoxicity were again more common with nintedanib approximately 7% versus 1.6%.

Deaths: The incidence of fatal AEs was lower in the nintedanib arms compared with the placebo arms (5.8% versus 7.3%). None of the deaths in the nintedanib arms were considered drug related by the investigators.

The incidence of serious AEs was comparable in the two treatment arms (30.4% versus 30.0%). Serious AEs occurring in more than 1% of subjects are listed in Attachment 2 Table 45. Serious gastrointestinal (3.0% versus 1.7%) and hepatobiliary disorders (1.1% versus 0.2%) were more common with nintedanib. There was also a slightly increased incidence of myocardial infarction (1.1% versus 0.5%).

Discontinuation due to an AE was more common with nintedanib than with placebo (19.3% versus 13.0%). Gastrointestinal events (diarrhoea, nausea) were more common with nintedanib as were hepatobiliary disorders and abnormal investigations (decreased weight and abnormal LFTs).

Adverse events of special interest (AESIs) are discussed in the CER; abdominal pain, arterial thromboembolism, MACE, hypertension and bleeding were increased in the nintedanib group, details are in Table 47 Attachment 2.

Laboratory investigations: Abnormal LFTs, increased creatinine were both increased in the nintedanib group. Abnormalities in other biochemical variables were similar between groups. There was an increased incidence in elevated mean corpuscular volume (MCV) (24.9% versus 9.4%). There was no significant difference in the abnormalities in vital signs.

Of the safety issues with major regulatory impact, hepatotoxicity in the IPF population was discussed. Hepatotoxicity was reversible; myocardial infarction was also increased (see Table 47 Attachment 2) in the nintedanib treated group.

Overall, the clinical evaluator states, ‘*in the pivotal IPF studies, nintedanib treatment resulted in only a small increase in the overall incidence of adverse events (95.5% versus 89.6%) with no increase in the incidence of serious AEs (30.4% versus 30.0%) and a small increase in the incidence of AEs classified as severe (27.3% versus 23.4%). There was no increase in the incidence of fatal AEs. The overall toxicity of the drug in IPF can therefore be considered to be modest. The proportion of subjects who had to discontinue treatment due to AES was modestly increased (19.3% versus 13.0%)*.’

##### Overall benefits

The clinical evaluator states that the benefit is ‘*A delay in disease progression, manifested by improved FVC compared to placebo’*.

##### Overall risks

The risks of nintedanib in the treatment of IPF identified are gastrointestinal toxicity, hepatotoxicity, hypertension, arterial thromboembolic events such as myocardial infarction, decreased weight, bleeding events and GI perforation.

##### Overall risk benefit assessment

The clinical evaluator states; ‘*For the treatment of mild to moderate IPF, the benefits of nintedanib are clinically significant, with a delay in the progression of a life threatening condition, for which there are currently no effective therapies available in Australia. This benefit is considered to outweigh the modest toxicity that the drug produces. The benefit-risk balance of nintedanib in this setting is therefore considered favourable’*.

##### Clinical evaluator’s recommendation

The evaluator stated that the overall risk benefit profile was favourable in the treatment of mild to moderate IPF.

### Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the RMP evaluator.

A suggested wording for the condition of registration concerning the RMP is:

Implement Vargatef EU-RMP version 2.1 dated 12 March 2015 (data lock point 15 February 2013) with Australian Specific Annex version 2.0 dated 26 March 2015; and Ofev EU-RMP Version 1.2 dated 30 December 2014 (data Lock Point 26 November 2013) with Australian Specific Annex version 2.0 dated 26 March 2015.

To this might be added words to the effect that updates or subsequent versions accepted by the TGA should also be implemented.

### Risk-benefit analysis

#### Issues – NSCLC

There was one pivotal study to support the use of nintedanib in treatment of locally advanced, metastatic or recurrent non-small cell lung cancer of adenocarcinoma tumour histology after first line chemotherapy, in combination with docetaxel as proposed. The study did not indicate that nintedanib adds appreciably to progression free survival (a statistically significant improvement did not, in the Dlegate’s opinion, reach clinical significance). However, there was an improvement in overall survival in the nintedanib + docetaxel arm, which cannot easily be discounted. The improvement was, on average, 2.3 months (from a median of 10.3 months in the docetaxel and placebo arm, to 12.6 months in the docetaxel and nintedanib arm), and this is in the Delegate’s opinion clinically significant.

This finding of an improvement in OS for the adenocarcinoma subgroup was made after a protocol amendment allowing for priority analysis of the adenocarcinoma subgroup. The initial approach would have been to consider all patients. There was some question about whether the change in approach was driven by early results of the study or Study 1199.0014; whether or not this is the case, it seems reasonable to consider OS in those subjects for whom the treatment is being proposed; that is those with adenocarcinoma, not other forms of NSCLC.

While the drug is being used in a palliative setting, there is some indication it will add to the burden on patients at this late stage by causing diarrhoea, nausea and vomiting; but there is also some indication that global health status does not deteriorate.

The wording of the indication in NSCLC is ambiguous, in that it may leave open use as maintenance where there has been no tumour progression with first line therapy. It should be specified that first line therapy must have failed before any use of nintedanib in combination with docetaxel. Appropriate wording is:

*OFEV is indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after failure of first line chemotherapy.*

The Delegate has recommended changes to the PI but these are beyond the scope of this AusPAR.

#### Delegate’s considerations

##### Non-small cell lung cancer (adenocarcinoma tumour histology)

One pivotal study (1199.13) supplies evidence in support of approval. The primary efficacy endpoint was progression free survival, and the reduction in risk of progression or death conferred by nintedanib was modest (to the point where the clinical significance of the effect can be questioned). A key secondary endpoint was overall survival; clinical significance of the overall survival benefit in the nintedanib arm is easier to accept (median OS in the nintedanib + docetaxel arm was 12.6 months; median in the placebo + docetaxel arm was 10.3 months).

Given the essentially palliative nature of treatment (second line treatment of advanced lung cancer), quality of life outcomes are very influential. Nintedanib causes diarrhoea which appears to impact on quality of life; there was no indication that the overall effect of nintedanib on quality of life was negative.

##### Idiopathic pulmonary fibrosis

The Delegate agrees with the clinical evaluator that the overall risk/benefit profile is acceptable to register nintedanib at 150 mg BD for ‘the treatment of IPF’.

The Delegate agrees that there should be no classification according to disease severity, mainly, as the current international consensus guideline does not recognise any formal staging or classification system for IPF disease severity. However the Delegate agrees with the clinical evaluator that delays regarding disease progression should be included in the Clinical Trials section (of the PI) only; this would be consistent with the approved indications in other jurisdictions (EU and FDA).

The concern is that there are no good quality data based on these studies on mortality. The FDA summary states that, ‘*in the analysis of all-cause mortality measured at vital status, mortality benefit was not demonstrated for the three studies individually or pooled. The numerical trend generally favoured nintedanib, but the confidence intervals were large’*.

The Delegate agrees with the evaluator that the results of the quality of life measures are not clinically significant; this should be specified in the PI.

#### Proposed action

The Delegate had no reason to say that the application for nintedanib should not be approved.

#### Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

##### Non-small cell lung cancer (adenocarcinoma histology)

1. Does the committee consider that the benefit-risk balance for the use of nintedanib proposed in this setting is favourable?
2. Can the committee suggest improvements to PI / CMI documents?

##### Idiopathic pulmonary fibrosis

1. Does the Committee agree with the Delegate that the risk/benefit profile is acceptable to allow registration of nintedanib 150 mg BD for the treatment of IPF?
2. Does the Committee agree with the Delegate and evaluator on the recommendations to the PI, discussed above (under Delegate’s issues)?

The committee is also requested to provide advice on any other issues relevant to a decision on whether or not to approve this application.

#### Response from sponsor

Presented here is the sponsor’s response to the Delegate’s proposed action in relation to our application to register the new chemical entity, Ofev/ Vargatef nintedanib (as nintedanib esilate) 100 mg and 150 mg soft capsules.

##### Sponsor’s comments on the delegate’s questions to the ACPM

The sponsor supports the Delegate’s Pre-ACPM preliminary assessment that ‘*The Delegate had no reason to say that the application for nintedanib should not be approved*.’ Furthermore, the sponsor is of the opinion that the benefit-risk balance for the use of nintedanib is favourable to support the proposed indications for use in NSCLC and IPF:

*OFEV is indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non*‐*small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after failure of first line chemotherapy.*

*OFEV is also indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF).*

The sponsor has updated the proposed PI based on the recommendations made by the Delegate, nonclinical and clinical evaluators, and has included newly available safety data.

##### Sponsor’s comments on the issues raised by the delegate

###### Non-small cell lung cancer (adenocarcinoma histology)

*‘One pivotal study (1199.13) supplies evidence in support of approval. The primary efficacy endpoint was progression free survival, and the reduction in risk of progression or death conferred by nintedanib was modest (to the point where the clinical significance of the effect can be questioned). A key secondary endpoint was overall survival; clinical significance of the overall survival benefit in the nintedanib arm is easier to accept (median OS in the nintedanib + docetaxel arm was 12.6 months; median in the placebo + docetaxel arm was 10.3 months).*

*Given the essentially palliative nature of treatment (2nd line treatment of advanced lung cancer), quality of life outcomes are very influential. Nintedanib causes diarrhoea which appears to impact on quality of life; there was no indication that the overall effect of nintedanib on quality of life was negative.’*

Sponsor comments:

In line with the OS benefit observed for the entire adenocarcinoma patient population, a median survival improvement by 3.0 months for those adenocarcinoma patients who progressed during or shortly after first line therapy represents a clinically meaningful survival benefit for these patients with worse prognosis. In these patients, median PFS was almost tripled. Even patients who were resistant to first line treatment and who had only progressive disease as best response during first line treatment showed a median OS improvement by 3.5 months in an exploratory analysis of Study 1199.0013.

Patients receiving nintedanib plus docetaxel reported a statistically significant, small deterioration in the symptom assessment of diarrhoea used in the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30. This finding did not compromise patients’ self-reported Global health status/Quality of life. Patients receiving nintedanib plus docetaxel reported statistically significant improvements in other individual lung cancer symptoms (for example pain in chest and pain in arm and shoulder). Diarrhoea was mostly of mild intensity and permanent discontinuation of study treatment due to diarrhoea occurred in 0.9% of adenocarcinoma patients.

###### Idiopathic pulmonary fibrosis

*The Delegate agrees with the clinical evaluator that the overall risk/benefit profile is acceptable to register nintedanib at 150 mg BD for ‘the treatment of IPF’.*

*The Delegate agrees that there should be no classification according to disease severity, mainly, as the current international consensus guideline does not recognise any formal staging or classification system for IPF disease severity. However, the Delegate agrees with the evaluator that delays regarding disease progression should be included in the CTs section only; this would be consistent with the approved indications in other jurisdictions (EU and FDA). The concern is that there are no good quality data based on these studies on mortality. The FDA summary states that, ‘in the analysis of all-cause mortality measured at vital status, mortality benefit was not demonstrated for the three studies individually or pooled. The numerical trend generally favoured nintedanib, but the confidence intervals were large’.*

*The Delegate agrees with the clinical evaluator that the results of the quality of life measures are not clinically significant; this should be specified in the PI.*

Sponsor comments:

The sponsor supports the clinical evaluator and the Delegate’s recommendation to register nintedanib at 150 mg BD for the ‘Treatment of IPF’ and has deleted ‘…*and to slow disease progression*’ from the proposed IPF indication.

The sponsor agrees to include a statement that the results of the quality of life measures are not clinically significant. The proposed PI now includes the following statement: ‘*The clinical significance of this finding is unknown*’.

##### Questions for the sponsor raised by the TGA delegate

*Pharmacokinetics (PK)*

*Nintedanib is metabolised by esterases to the metabolite BIBF 1202, which is then glucuronidated by UGT enzymes; neither metabolite is thought to contribute to clinical effects. The non‐clinical evaluation report noted a lack of studies of potential pharmacological activity of the BIBF 1202 glucuronide; the sponsor has supplied top‐line information to the effect that the BIBF 1202 glucuronide metabolite does not appreciably inhibit VEGFR 1‐3, FGFR 1‐4 and PDGFR α and β. Could the sponsor please supply the cited data?*

Sponsor comments:

The sponsor has provided the complete dataset that supports the information that was provided in the response to the issues raised by the nonclinical evaluator.

*Pharmacokinetics (PK)*

*There were no completed specific studies of nintedanib PK in hepatic impairment. The sponsor should undertake to provide completed* [clinical study reports] *CSRs of studies examining the effects of hepatic impairment in PK of nintedanib as the CSRs become available.*

Sponsor comments:

The sponsor acknowledges the Delegate’s comment. Investigations of the PK of nintedanib in patients with impaired liver function classified by Child Pugh criteria have become available. They comprise data from two studies in patients with hepatocellular carcinoma (HCC) (1199.37 and 1199.39) and data from a dedicated single dose Phase I study with nintedanib in volunteers with and without liver impairment (1199.200).

An application to include this data in the EU SmPC is currently under review by EMA. The sponsor provides an assurance that a similar application will be submitted to the TGA following registration of nintedanib.

In summary, the exposure of nintedanib increased with increasing impairment of hepatic function across all investigations. Compared to healthy controls, nintedanib exposure in Study 1199.200 based on Cmax and AUC increased by approximately:

* + 2.2 fold in subjects with mild liver impairment defined as Child Pugh category A and
  + 7.6 fold and 8.7 fold, respectively, in subjects with moderate liver impairment defined as Child Pugh category B.

Observations in patients with cancer were in line with data in volunteers with an increase of nintedanib exposure for HCC patients of Child Pugh category A (1199.37) of 1.7 fold compared to cancer patients without hepatic impairment from an independent study.

*Pharmacokinetics (PK)*

*The nonclinical evaluation report also noted that nintedanib inhibited UGT, which may influence the PK of drugs predominantly metabolised by glucuronidation. Report U06-1744 (in vitro data) concluded that clinically relevant interactions are likely to be rare, because inhibition was seen at a high concentration and also because few drugs depend for their clearance solely on glucuronidation; effects were only tested for UGT1A1 and 2B7. However, the nonclinical evaluator considered it would be useful to understand whether the metabolite BIBF 1202 glucuronide affects UGT enzymes. The sponsor has provided clarification about this issue proposing to supply data post registration. Could the sponsor clarify whether there may be inhibition of other relevant UGT isoforms, by the parent drug or its metabolites?*

Sponsor comments:

The investigations proposed by the sponsor are ongoing. Preliminary data indicate that there was no pronounced inhibition of UGT1A1 catalysed estradiol 3-glucuronidation and UGT 2B7 catalysed azidothymidine glucuronidation by BIBF 1202-glucuronide up to 100 µM, which was the highest concentration tested. Thus BIBF 1202-glucuronide does not interact with the two most relevant UGT (UGT1A1 and 2B7) enzymes for the glucuronidation of drugs.

*Efficacy in lung cancer, dosage selection:*

*Dosage selection for the pivotal NSCLC trial is considered in the review of Phase 1 Study 1199.0004. The maximum tolerated dose was considered to be 200 mg BD. The sponsor reached the same conclusion about the MTD after review of Phase I studies 1199.1, 1199.2 and 1199.3. Phase II Study 1199.0010 of nintedanib monotherapy in NSCLC found no differences in efficacy between 150 mg BD and 250 mg BD dosing. Could the sponsor clarify why 150 mg BD dosing was not tested in pivotal studies (of NSCLC)?*

Sponsor comments:

The dose finding of anti-cancer compounds is generally based on the paradigm that the MTD should be defined in order to expose the tumour to the highest achievable dose by maintaining a tolerable safety for the patients. The dose finding for nintedanib for the treatment of cancer patients followed this approach, but also took into account the entire safety and efficacy data available at that point in time.

A wide range of nintedanib monotherapy doses were investigated in Phase I and II trials, from 50 to 450 mg QD and from 150 to 300 mg BD In Phase I dose escalation trials (Trials 1199.1, 1199.2, and 1199.3), the MTD was determined as 250 mg BD The predominant dose limiting toxicities were gastrointestinal (GI) AEs and fully reversible elevations in liver enzymes (ALT, AST, GGT) not accompanied by relevant bilirubin increases. Based on the nintedanib monotherapy data, a dose threshold for liver enzyme increases was observed at approximately 250 mg BD, with higher frequencies of liver enzyme increases at nintedanib doses > 200 mg BD compared to doses of ≤ 200 mg BD. According to data from the Trials 1199.1, 1199.2, and 1199.3, splitting the cumulative daily dose into 2 doses per day increased the tolerability of nintedanib, compared with once daily dosing. In Phase I trials combining nintedanib with pemetrexed, docetaxel, paclitaxel/carboplatin, or mFOLFOX6 (Trials 1199.4, 1199.5, 1199.6, 1199.18, 1199.51), the recommended dose of nintedanib was established as 200 mg BD The pattern of AEs was comparable to the AE profile observed in Phase I monotherapy trials except for the chemotherapy related AEs. Based on the overall safety profile from all Phase I and Phase II studies, a nintedanib dose of 200 mg BD was selected for the combination with standard therapy of docetaxel (75 mg/m2) or pemetrexed (500 mg/m2) in the Phase III trials 1199.13 and 1199.14. This starting dose could be reduced in 2 steps from 200 mg BD to 150 mg BD and then to 100 mg BD in case of intolerable AEs.

Study 1199.10 was a small exploratory two arm, double blind Phase II trial investigating the safety and the efficacy of 250 mg nintedanib BD versus 150 mg of nintedanib BD monotherapy in advanced NSCLC patients. A total of only 73 patients were enrolled. Although the efficacy in terms of PFS and OS benefit were similar between both arms, the number of patients treated at 150 mg BD was too small to serve as a basis for the definition of the Phase III dose provided that in the pivotal trials the combination of nintedanib with docetaxel or pemetrexed was being investigated.

Furthermore, exposure response analyses were performed based on PK, safety, and efficacy data from Study 1199.13 which are provided with this response. From a safety perspective, there was a shallow relationship between nintedanib exposure and the occurrence of ALT/AST elevations of any grade which were generally manageable with dose interruption and dose reduction. There was no relationship between nintedanib exposure and high severity ALT/AST elevations or diarrhoea within the Phase III exposure range. With respect to efficacy, the hazard ratios for PFS and OS did not show a monotonic, for example linear dependency to exposure; however a trend towards longer OS and PFS was observed for the highest exposure group. Therefore, maximising exposure in a given patient seems desirable from a benefit-risk perspective and supports the use of 200 mg nintedanib BD as starting dose with the option to adapt according to the proposed dose reduction schemes.

In conclusion, based on the results of the dose finding studies and the overall safety profile of the compound beyond the background that in any case a potential under treatment of cancer patients should be avoided, 200 mg BD of nintedanib was chosen as the Phase III dose. The results in Study 1199.13 confirm that 200 mg BD in combination with docetaxel is an efficacious and tolerable dose for advanced NSCLC patients of adenocarcinoma tumour histology. In order to ensure the safety of the patients a detailed dose reduction scheme is in place in the PI.

*Efficacy in lung cancer, Pivotal Study 1199.0013:*

*In the final OS analysis for Study 1199.13, subsequent use of anti‐cancer drugs is fairly balanced, but there is some imbalance in use of investigational anti‐cancer drugs (1.2% for placebo arm, 4.7% for nintedanib arm, in the adenocarcinoma subset). The sponsor should clarify whether anti‐PD‐1 antibodies were used, as these have shown efficacy in second line NSCLC.*34

Sponsor comments:

Only a few patients with adenocarcinoma histology were treated with an investigational compound when they discontinued study treatment (the lists of the investigational compounds that were used were provided). There were 15 (4.7%) patients in the nintedanib arm and 4 (1.2%) patients in the placebo arm who received an investigational compound as third line treatment. None of the patients in either arm received nivolumab as subsequent treatment. Thus far, none of the other investigational compounds have shown a survival benefit in Phase III studies. In conclusion, the consistent and clinically meaningful OS benefit observed for the adenocarcinoma patients in Study 1199.13 is not influenced by the administration of subsequent anti-PD L1 compounds.

*Safety in lung cancer:*

*The sponsor is invited to comment on likely mechanisms resulting in diarrhoea, in the light of rat data indicating dose dependent inhibition of gastrointestinal tract motility yet symptomatic use of loperamide in clinical trials. Is there objective evidence that anti motility agents are beneficial in the treatment of nintedanib induced gastrointestinal toxicity?*

Sponsor comments:

In safety pharmacology studies of GI functions, single oral doses of 10, 30 and 100 mg/kg nintedanib have been administered. Exposure achieved at these dose levels in rats (estimates based in toxicokinetic data from animals of the same rat strain from repeat dose toxicity studies) is below (at 10 mg/kg), close to (at 30 mg/kg) or above (at 100 mg/kg) that at the maximum recommended human dose of 200 mg twice daily.

The dose levels of 10 mg/kg and 30 mg/kg induced no effects on gastric emptying. At 100 mg/kg a significant inhibition of gastric emptying was observed.[[35]](#footnote-36) GI transit was not influenced at 10 mg/kg, but at 30 mg/kg and 100 mg/kg intestinal transit was dose dependently reduced.[[36]](#footnote-37)

Intraduodenal administration of the same doses had no effect on gastric acid output, total acidity, gastric pH and volume.[[37]](#footnote-38).

In repeat dose toxicity studies, in rats, dogs, Cynomolgus and Rhesus monkeys, there was no evidence for an increase in the contents of the stomach and the intestine. Based on the overall lack of unequivocal histopathological lesions, clinical signs and gross findings at necropsy were considered to be rather in agreement with an increased peristalsis and/or a decrease in water absorption.

Based on these nonclinical data, the assumption that the co administration of nintedanib and loperamide may have a beneficial effect on the clinical signs in animals appears to be reasonable. Nonclinical studies with combination of nintedanib/loperamide and/or of the potential pathomechanism of diarrhoea in animals have not been conducted.

The protocol of Study 1199.13 includes the following recommendations for management of diarrhoea*: ‘Treatment of diarrhoea (common terminology criteria for adverse events (CTCAE) grade 2 or greater) with for example loperamide according to the recommended dose schedule. Temporary interruption of nintedanib, if diarrhoea of CTCAE grade 2 continues for more than seven consecutive days despite supportive care or diarrhoea is of CTCAE grade 3 or greater. After interruption, treatment could be resumed at a reduced dose.’*

In the overall population of Study 1199.13, 276 (42.6%) patients treated with nintedanib experienced diarrhoea, with the majority, 264 (40.5%) patients, recovering from the AE. Treatment was required in 184 (28.2%) patients. Forty seven (7.2%) patients reduced the dose of nintedanib and 8 (1.2%) patients discontinued last study medication due to diarrhoea. The high rate of recovery and low number of discontinuations indicate that the recommended management of diarrhoea was effective.

*Issues – NSCLC:*

*The wording of the indication in NSCLC is ambiguous, in that it may leave open use as maintenance where there has been no tumour progression with first line therapy. It should be specified that firstline therapy must have failed before any use of nintedanib in combination with docetaxel. Appropriate wording is:*

*OFEV is indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after failure of first line chemotherapy.*

Sponsor comments:

The sponsor agrees with the Delegate’s recommended wording and has revised the PI accordingly.

#### Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Ofev and Vargatef soft gel capsules, containing 100 mg and 150 mg of nintedanib esilateto have an overall positive benefit–risk profile for the Delegate’s amended indications**;**

*OFEV is indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after failure of first line chemotherapy.*

*OFEV is also indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF).*

In making this recommendation the ACPM;

* Advised that the indication for NSCLC should state ‘*after failure of first line therapy*’ to prevent use as maintenance therapy.
* Expressed concern about the toxicity of nintedanib as it only provided limited benefit in patients with NSCLC.
* Advised that removal of *‘to slow disease progression*’ from the indication for IPF was appropriate.
* Provision of the results of overall survival from the clinical trials for IPF.

##### Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

##### Specific advice

The ACPM advised the following in response to the Delegate’s specific questions on this submission:

###### Non-small cell lung cancer (adenocarcinoma histology) (NSCLC)

1. *Does the committee consider that the benefit-risk balance for the use of nintedanib proposed in this setting is favourable?*

The ACPM noted that accepting the efficacy of nintedanib hinges on the validity of the statistical analysis of the subgroup. The ACPM noted that although the pivotal study (1199.0013) did meet its primary efficacy endpoint PFS, 3 weeks PFS was not a clinically meaningful result. In addition, there was no overall survival benefit in the overall population. The ACPM advised that if the subgroup analysis is accepted, then there is a small clinically uncertain improvement in survival for patients with adenocarcinoma with PFS prolonged from 2.7 months to 3.5 months; however the approximately 2 month overall survival advantage demonstrated in the nintedanib arm, although also small, is clinically meaningful in the second line setting for adenocarcinoma of the lung. However there was concern about the toxicity of nintedanib, particularly when used in combination with docetaxel, and how this affected quality of life of patients particularly in the second line setting. Nonetheless, overall the ACPM considered that toxicity could be managed by current treatment algorithms. Therefore, the ACPM advised the risk-benefit of nintedanib in NSCLC of adenocarcinoma histology in the second line setting is favourable.

1. *Can the committee suggest improvements to PI/CMI documents?*

The ACPM advised that it agreed with the Delegate’s amendment to the indication for NSCLC that is, the addition of ‘*after failure of first line chemotherapy’*, which will prevent use as maintenance therapy.

###### Idiopathic pulmonary fibrosis

1. *Does the Committee agree with the Delegate that the benefit-risk profile is acceptable to allow registration of nintedanib 150 mg BD for the treatment of IPF?*

The ACPM expressed concern whether the primary endpoint, FVC, was an appropriate surrogate endpoint. The ACPM noted that the pivotal studies (combined) met their primary endpoint (decline in FVC) and showed a significant reduction in drop in FVC, but did not show a survival advantage. However, the ACPM noted that there is some evidence to suggest that improvements in FVC can translate into a survival advantage. The ACPM further noted that the QoL results were not affected by the treatment and were not likely to be meaningful. The ACPM expressed disappointment that no survival improvement was demonstrated and there was no convincing QoL data. However, the ACPM noted that overall toxicity was low and that there were no other treatment options available for patients with IPF. The ACPM advised that although efficacy was modest the benefit-risk profile of nintedanib for the treatment of IPF is acceptable. The ACPM requested that the sponsor provide data on survival when available as a condition of registration.

1. *Does the Committee agree with the Delegate and evaluator on the recommendations to the PI, discussed above (under Delegate’s issues)?*

The ACPM advised that it agreed with the Delegate’s amendments to the indication for IPF as there were no data submitted to support the claim that nintedanib slowed disease progression.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

### Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ofev/Vargatef nintedanib (as esilate) 100mg and 150 mg soft capsule for oral use, indicated for:

*Ofev/Vargatef is indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after failure of first line chemotherapy.*

*Ofev/Vargatef is also indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF).*

#### Specific conditions of registration applying to these goods

Vargatef EU-RMP version 2.1 dated 12 March 2015 (data lock point 15 February 2013) with Australian Specific Annex version 2.0 dated 26 March 2015; and Ofev EU-RMP Version 1.2 dated 30 December 2014 (data Lock Point 26 November 2013) with Australian Specific Annex version 2.0 dated 26 March 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

## Attachment 1. Product Information

The PI approved for Ofev at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>. The PI for Vargatef is identical except for the product name.

## Attachment 2. Extract from the Clinical Evaluation Report

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| Therapeutic Goods Administration |
| PO Box 100 Woden ACT 2606 Australia  Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605  [**https://www.tga.gov.au**](https://www.tga.gov.au) |

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