Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Nintedanib (as Esilate)

Proprietary Product Name: Ofev/Vargatef

Sponsor: Boehringer Ingelheim Pty Ltd

February 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate aminotransferase
BID	Twice daily (Latin: *bis in die*)
CI	Confidence interval
CTD	Connective tissue disease
DBL	Database lock
DLCO	Carbon monoxide diffusion capacity
EU	European Union
FVC	Forced vital capacity
HR	Hazard ratio
HRCT	High resolution computed tomography
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
K-BILD	King's Brief Interstitial Lung Disease Questionnaire
NSCLC	Non-small cell lung cancer
NSIP	Non-specific interstitial pneumonia
PBRER(s)	Periodic benefit–risk evaluation report(s)
PF-ILD	Interstitial lung diseases with a progressive phenotype
PI	Product Information
PK	Pharmacokinetic(s)
PSUR	Periodic safety update report
SSc-ILD	Systemic sclerosis-associated interstitial lung disease
TGA	Therapeutic Goods Administration

Abbreviation	Meaning
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
USA	United States of America

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications, variation to register entry resulting in a change of product information requiring evaluation of clinical, nonclinical, or bioequivalence data
Product names:	Ofev/Vargatef
Active ingredient:	Nintedanib (as esilate)
Decision:	Approved
Date of decision:	23 December 2020
Date of entry onto ARTG:	5 January 2021
ARTG numbers:	226065, 226066, 226067 and 226068
▼ *Black Triangle Scheme:*[1]	No
Sponsor's name and address:	Boehringer Ingelheim Pty Limited 78 Waterloo Road 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 also indicated for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.*
Route of administration:	Oral
Dosage:	**Non-small cell lung carcinoma** Treatment with Ofev should be initiated and supervised by a physician experienced in the use of anticancer therapies. The recommended dose of Ofev is 200 mg twice daily (BID) administered approximately 12 hours apart, on Days 2 to 21 of a standard 21-day docetaxel treatment cycle.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Ofev must not be taken on the same day of docetaxel chemotherapy administration (that is, Day 1).

The recommended maximum daily dose of 400 mg should not be exceeded.

Patients may continue therapy with Ofev after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs.

For dosage, method of administration and dose modifications of docetaxel, please refer to the corresponding product information for docetaxel.

Idiopathic pulmonary fibrosis, other chronic fibrosing interstitial lung disease with a progressive phenotype, and systemic sclerosis associated interstitial lung disease

Treatment should be initiated by physicians experienced in the diagnosis and treatment of conditions for which Ofev is indicated.

The recommended dose of Ofev is 150 mg BID administered approximately 12 hours apart.

The recommended maximum daily dose of 300 mg should not be exceeded.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Boehringer Ingelheim Pty Limited (the sponsor) to register Ofev/Vargatef (nintedanib (as esilate)) 100 mg and 150 mg, soft capsule for the following proposed extension of indications:

> *Treatment of other chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype (PF-ILD).*

The term interstitial lung disease encompasses a heterogeneous group of diseases which are characterised by diffuse inflammation and fibrosis of the lung parenchyma.[2] According to the American Thoracic Society, the term encompasses more than 200 lung disorders.[3]

A subgroup of patients with ILD exhibit a phenotype of progressive fibrosis, with increasing symptoms, worsening quality of life, declining lung function and reduced survival. The umbrella term interstitial lung disease with a progressive phenotype has been applied to this subgroup. This term includes subjects with a variety of disease entities. However many of these diseases have similarities in pathogenesis and clinical behaviour and therefore a potential for common treatments.[2, 4, 5]

Idiopathic pulmonary fibrosis (IPF) is the most common form of ILD that displays a progressive phenotype. Other ILDs that may exhibit a progressive pattern include connective tissue disease (CTD)-associated ILD, fibrotic hypersensitivity pneumonitis, unclassifiable ILD and idiopathic non-specific interstitial pneumonia (NSIP).[2, 5]

Risk factors for an increased likelihood of progression include male sex, increased age, lower forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLCO) at Baseline and a 'usual interstitial pneumonia' or 'UIP' pattern on radiological imaging.[2]

The features of UIP are:[6]

- Honeycombing, clustered cystic air spaces, 3 to 10 mm in diameter with thick, well defined walls. It often presents as multiple layers of subpleural cysts on top of each other, but may also present as a single layer;
- traction bronchiectasis, ranging from subtle irregularity and non-tapering of the bronchial / bronchiolar wall to marked airway distortion and varicosity; and
- ground glass opacification, a hazy increased opacity of lung with preservation of the bronchial and vascular markings. The ground glass opacification is superimposed on a fine reticular pattern.

UIP is the hallmark radiological pattern for IPF;[6] but can also be present with other forms of ILD.[7]

There are currently no approved pharmacological therapies for non-IPF ILDs. Immunosuppressive agents are used to treat some forms of disease such as CTD-associated ILD, fibrotic hypersensitivity pneumonitis and unclassifiable ILD. Agents used include prednisone, mycophenolate, azathioprine, methotrexate and cyclosporin. Non-pharmacological treatments include avoidance of precipitating factors (smoking, antigens, occupational exposures and so on), pulmonary rehabilitation, oxygen therapy and lung transplantation.[2]

The clinical rationale for the use of nintedanib in PF-ILDs was stated as follows in the sponsor's clinical overview, given below:

> *'The working hypothesis is that the response to lung injury in these patients includes the development of fibrosis, which becomes progressive, self-sustaining, and independent of*

[2] Wong, A. W. et al. Progression of Fibrosing Interstitial Lung Disease, *Respir Res*, 2020; 21 (1): 32.
[3] American Thoracic Society. Breathing in America: Diseases, Progress, and Hope. (Accessed on 02 November 2020).
[4] Collins, B. F. and Raghu, G. Antifibrotic Therapy for Fibrotic Lung Disease Beyond Idiopathic Pulmonary Fibrosis, *Eur Respir Rev*, 2019; 28 (153): 190022.
[5] Cottin, V. Treatment of Progressive Fibrosing Interstitial Lung Diseases: a Milestone in the Management of Interstitial Lung Diseases, *Eur Respir Rev*, 2019; 28 (153): 190109.
[6] Raghu, G. et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline, *Am J Respir Crit Care Med*, 2018; 198 (5): e44-e68.
[7] Wuyts. W. A. et al. Differential Diagnosis of Usual Interstitial Pneumonia: When Is It Truly Idiopathic? *Eur Respir Rev*, 2014; 23: 308–319

the original clinical association or trigger. It was postulated that, at this stage, targeted anti-fibrotic therapy is required to slow the progression of the disease. With the exception of IPF, for which nintedanib and pirfenidone are available, there is no approved therapy for other chronic fibrosing ILDs with a progressive phenotype. Based on the similarity in both the underlying pathophysiology and clinical course with IPF, it was anticipated that nintedanib elicits comparable effects in patients with progressive fibrosing ILDs as demonstrated in IPF.'

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 1 September 2015 for the below 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 indicated for the treatment of idiopathic pulmonary fibrosis (IPF). Ofev is also indicated for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype. Ofev is indicated for slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).*

At the time the TGA considered this application, a similar application was approved in the European Union (EU) (approved 13 July 2020), the United States of America (USA) (approved 9 March 2020), Canada (approved 20 May 2020) and Switzerland (approved 1 October 2020); and under consideration in Singapore (submitted 30 March 2020).

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
EU	27 August 2019	Approved 13 July 2020	*Ofev is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.*
USA	9 September 2019	Approved 9 March 2020	*Treatment for chronic fibrosing interstitial lung diseases with a progressive phenotype.*
Canada	25 October 2019	Approved 20 May 2020	*Ofev (nintedanib) is indicated for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (also known as progressive fibrosing ILD).*
Singapore	30 March 2020	Under consideration	Under consideration

Region	Submission date	Status	Approved indications
Switzerland	25 October 2019	Approved 1 October 2020	*Ofev is also indicated for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR 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. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-04480-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	3 January 2020
First round evaluation completed	29 May 2020
Sponsor provides responses on questions raised in first round evaluation	30 July 2020
Second round evaluation completed	31 August 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 November 2020
Sponsor's pre-Advisory Committee response	17 November 2020
Advisory Committee meeting	3 December 2020
Registration decision (Outcome)	23 December 2020
Completion of administrative activities and registration on the ARTG	5 January 2021
Number of working days from submission dossier acceptance to registration decision*	223

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

Nintedanib binds competitively to the adenosine triphosphate binding pocket of several kinases involved in the pathogenesis of fibrotic tissue remodelling and blocks the intracellular signalling.

Nintedanib has been approved for slowing the rate of decline in pulmonary function in patients with SSc-ILD. The current submission is to extend the indications of nintedanib for the treatment of other chronic fibrosing PF-ILDs. Data supporting the SSc-ILD indication are also supportive of this extension to indications.

In mouse models of chronic hypersensitivity pneumonitis, nintedanib treatment significantly reduced the pulmonary accumulation of white blood cells, attenuated inflammatory mediators in lung homogenates and reduced lung tissue collagen-1 and alpha-smooth muscle actin content.

In a well established mouse model of rheumatoid arthritis associated ILD like mouse induced by zymosan nintedanib 60 mg/kg/day had divergent effects. When treatment was started when both joint swelling and interstitial pneumonia were still developing, nintedanib reduced joint swelling by 50%, but did not reduced pulmonary fibrosis. On the contrary, when treatment was started when the arthritis pathology reached its maximum, nintedanib reduced pulmonary fibrosis (reduction of lung hydroxyproline by 33%, and increased lymphocytes and infiltrating macrophages ($CD11c^{var}CD11b^{+}F4/80^{+}$) approximately 2 to 3 fold compared with untreated control, without affecting joint swelling.

Nintedanib was also tested in a mouse model of collagen-induced arthritis, due to its capacity to inhibit some growth factor receptors involved in angiogenesis. Nintedanib had no effect on the progression of rheumatoid arthritis.

There are no nonclinical objections to the new indication for the treatment of other chronic fibrosing PF-ILDs.

The proposed PI document is considered acceptable.

Clinical

The clinical dossier consisted of one pivotal Phase III trial.

Pharmacology

Pharmacokinetics

Trough plasma concentrations of nintedanib were measured at two time points during the one pivotal study included in the submission. The pharmacokinetics (PK) findings were consistent with those previously observed for nintedanib.

Exposure response analyses for efficacy (decline in FVC) and safety (aspartate aminotransferase (AST) / alanine aminotransferase (ALT) elevations) in the new patient population were also presented. A relationship between nintedanib exposure and the rate of decline in FVC was demonstrated. The relationship was generally consistent with that observed in IPF subjects.

A relationship between nintedanib exposure and the risk of elevations in AST or ALT (to ≥ 3 x the upper limit of normal (ULN)) was also demonstrated. This relationship had been established in previous analyses.

Pharmacodynamics

No new pharmacodynamic data were submitted.

Efficacy

The dosing regimen chosen for the pivotal study was 150 mg twice daily (BID). The choice was based on the findings of the studies conducted in IPF, where this dose was found to be effective and safe.

Data to support the efficacy of nintedanib for the proposed new indication came from a single pivotal Phase III trial, Study 1199.247 (also known as the INBUILD trial).

Study 1199.247 (the INBUILD trial)

This was a multicentre, multinational, prospective, randomised, placebo controlled, double blind, parallel design clinical trial to investigate the efficacy and safety of nintedanib in patients with PF-ILD over 52 weeks.

The objective of this trial was to investigate the efficacy and safety of 150 mg BID nintedanib in patients with PF-ILD compared to placebo over 52 weeks (Part A).

The primary objective was to demonstrate a reduction in lung function decline, as measured by the annual rate of decline in FVC for nintedanib compared to placebo over 52 weeks.

The main secondary objectives of the trial were to investigate the effect of nintedanib treatment on quality of life over 52 weeks using the King's Brief Interstitial Lung Disease Questionnaire (K-BILD);[8] and to assess the effect of nintedanib on time to first acute ILD exacerbation or death over 52 weeks and on overall survival alone over 52 weeks.

Other objectives included the assessment of other symptoms of the disease such as dyspnoea and cough, as well as the assessment of safety, tolerability, and PK of nintedanib.

Subjects were required to have a diagnosis of an ILD with evidence of fibrosis on high resolution computed tomography (HRCT) and evidence of disease progression. Enrolment was restricted to subjects with a DLCO of ≥ 30% and < 80%, and an FVC of ≥ 45% of predicted. Subjects with IPF were excluded.

Subjects were randomised in a 1 to 1 ratio to receive either nintedanib 150 mg BID or matching placebo orally. In the event of toxicity, the dose could be reduced to 100 mg BID temporarily or permanently, or treatment could be interrupted.

The main analysis of trial was performed after the last randomised patient had completed the Week 52 visit. The main benefit-risk assessment of nintedanib in patients with PF-ILD was based on efficacy and safety data over 52 weeks, that is data from part A of the trial. Additional data collected beyond 52 weeks.

[8] The King's Brief Interstitial Lung Disease (K-BILD) is a 15-item validated health-related quality of life (HRQOL) questionnaire. The method of scoring the K-BILD has recently changed to incorporate a logit-scale transformation from one that used raw item responses, as this is potentially a more linear scale.

Part B and available at the database lock (DBL)1 snapshot were included in the main analysis as supportive information. Evaluations over the whole trial (Parts A and B) included time-to-event efficacy endpoints and safety analyses.

There were two co-primary populations defined for the analyses in this trial:

- all patients (the overall population); and
- patients with HRCT with UIP-like fibrotic pattern.

A total of 1010 subjects were screened for the trial. Of these, 663 were randomised and treated, 331 to placebo and 332 to nintedanib. The randomised set and treated set were identical for each of the two study arms. In the placebo arm, 85.2% of subjects completed 52 weeks of treatment compared to 75.9% in the nintedanib arm. Reasons for discontinuation were adverse events, withdrawal by the patient, other reasons, protocol deviations, and loss to follow-up. Discontinuations due to adverse events were more common in the nintedanib arm (19.6% versus 10.3%). Overall, 65.7% of patients in the nintedanib group and 69.8% of patients in the placebo group completed the planned treatment. Overall, the two treatment arms were well balanced with respect to these baseline factors.

Results: In the overall population, the adjusted annual rate of decline in FVC over 52 weeks was lower in the nintedanib group (-80.82 mL/year) than in the placebo group (-187.78 mL/year). The adjusted difference between the treatment groups was 106.96 mL/year (95% confidence interval (CI): 65.42 to 148.50; $p < 0.0001$).

Patients with high resolution computed tomography with usual interstitial pneumonia like fibrotic pattern

Of the 412 patients with HRCT with UIP like fibrotic pattern, 206 patients received nintedanib and 206 received placebo. In the co-primary population of patients with HRCT with UIP like fibrotic pattern, the adjusted annual rate of decline in FVC over 52 weeks was lower in the nintedanib group (-82.87 mL/year) than in the placebo group (-211.07 mL/year). The adjusted difference between the treatment groups was 128.20 mL/year (95% CI: 70.81 to 185.59; $p < 0.0001$).

Patients with other high resolution computed tomography fibrotic patterns

In the complementary population of patients with other HRCT fibrotic patterns, the adjusted annual rate of decline in FVC over 52 weeks was lower in the nintedanib group (-78.97 mL/year) than in the placebo group (-154.24 mL/year). The adjusted difference between the treatment groups was 75.28 mL/year.

In the primarily analysis, the statistical model assumed that patients who discontinued from the study prematurely would have behaved similarly to those who remained in the study. A sensitivity analysis was conducted in which only on-treatment measurements of FVC were used in the model. The results were consistent with the findings of the primary analysis.

Results in subgroups depending on gender, age group, race, baseline FVC % predicted, and underlying clinical ILD diagnosis (grouped) for overall population. For the co-primary population of patients with HRCT with UIP-like fibrotic pattern, the subgroups were defined by gender, age group, and race. Furthermore, an additional analysis investigated the impact of the underlying ILD diagnoses by employing the method of excluding ILD diagnosis groups one by one was performed. There were no major differences in treatment effects were observed. The direction of effect estimates for all analysed subgroups appeared consistent with the overall effect.

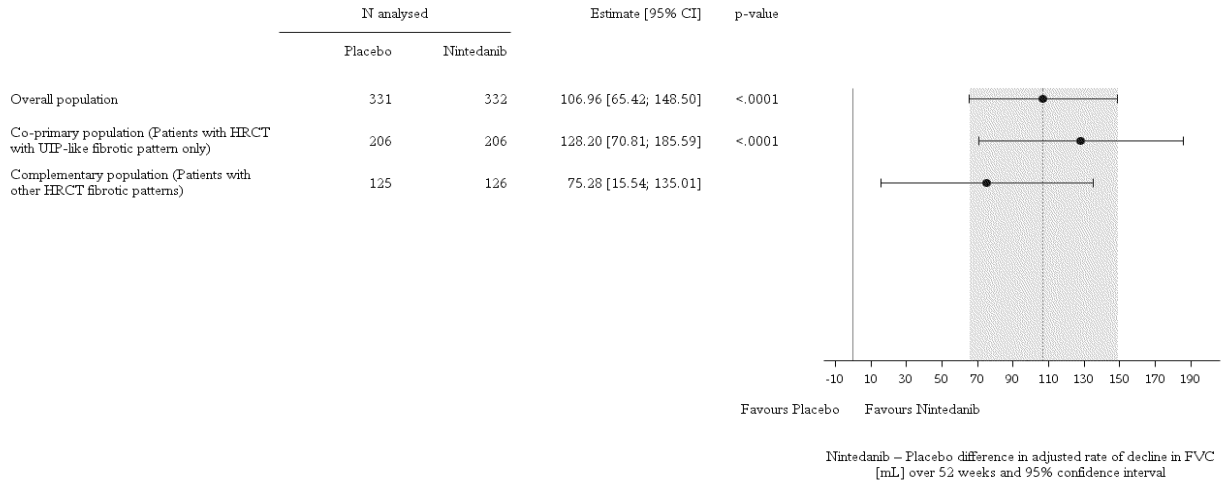
Table 3: Study 1199.247 Annual rate of decline in forced vital capacity (mL/year) over 52 weeks (in the treated set)

Treatment	Number analysed	Rate of FVC decline over 52 weeks: Adjusted rate[1]	SE	95% CI	Comparison vs. placebo: Adjusted difference[1]	SE	95% CI	p-value
Overall population								
Placebo	331	-187.78	14.84	(-216.92, -158.64)				
Nintedanib 150 mg bid	332	-80.82	15.07	(-110.42, -51.22)	106.96	21.15	(65.42, 148.50)	<0.0001
Patients with HRCT with UIP-like fibrotic pattern								
Placebo	206	-211.07	20.49	(-251.38, -170.77)				
Nintedanib 150 mg bid	206	-82.87	20.76	(-123.73, -42.02)	128.20	29.17	(70.81, 185.59)	<0.0001
Patients with other HRCT fibrotic patterns								
Placebo	125	-154.24	21.20	(-196.02, -112.47)				
Nintedanib 150 mg bid	126	-78.97	21.64	(-121.60, -36.33)	75.28	30.32	(15.54, 135.01)	–[2]

[1].Based on a random coefficient regression with fixed effects for treatment, HRCT pattern (only for the overall population), and baseline FVC (mL), and including treatment-by-time and baseline-by-time interactions within patient errors were modelled by an unstructured variance covariance matrix.

[2] Normal p-value 0.0137

Figure 1: Study 1199.247 Results for the primary endpoint in the co-primary populations and the complementary population (primary analysis) – the treated set



Results for main secondary efficacy outcomes

King's Brief Interstitial Lung Disease Questionnaire total score

In the overall population, the adjusted mean of absolute change from baseline in K-BILD total score at Week 52 was small in either treatment group. The adjusted mean difference between treatment groups was 1.34 (95% CI: -0.31 to 2.98).

Time to first acute interstitial lung disease exacerbation or death

In the overall population, the incidence of an acute exacerbation or death event over 52 weeks was 9.7% in the placebo arm and 7.8% in the nintedanib arm. The hazard ratio was 0.80 (95% CI: 0.48 to 1.34).

In the subpopulation with a UIP-like pattern on HRCT, the incidence of events was 12.1% in the placebo arm and 8.3% in the nintedanib arm, with a hazard ratio of 0.67 (95%CI: 0.36 to 1.24).

Time to death

Results for the overall population over the first 52 weeks of the study deaths occurred in 5.1% of placebo-treated subjects and 4.8% of nintedanib treated subjects. The difference was not significant with a hazard ratio of 0.94 (95% CI: 0.47 to 1.86).

Results were similar in the subpopulation with a UIP-like pattern on HRCT –7.8% with placebo versus 5.3% with nintedanib; hazard ratio (HR) = 0.68 (95% CI: 0.32 to 1.47).

Safety

The only data to support the safety of nintedanib in the proposed new patient population come from the pivotal Study 1199.247. In this trial a total of 332 subjects were treated nintedanib, and 331 with placebo. Mean duration of exposure to nintedanib in the overall population was 15.58 months and 248 subjects received the drug for more than 12 months. This extent of exposure is considered adequate to assess safety in the proposed new population.

Over the whole trial, nintedanib treatment was associated with a small increase in the incidence of overall adverse events (AE) (98.2% versus 93.1%). However, there was no apparent increase in the severe AEs (27.1% versus 32.0%) or serious AEs (44.3% versus 49.5%). There was also no increase in fatal AEs (6.3% versus 10.9%) and there was a trend towards reduced overall mortality with nintedanib. Nintedanib treatment was associated with an increased incidence of AEs leading to discontinuation of treatment (22.0% versus 14.5%).

The pattern of nintedanib toxicity observed in the study was consistent with that previously documented for the drug. The major toxicities were: gastrointestinal disorders, especially diarrhoea but also nausea, vomiting, abdominal pain and decreased appetite; hepatotoxicity; weight loss; headache; and hypertension.

There was no notable increase in the incidence of arterial or venous thromboembolism, bleeding or neutropaenia in this study. The incidence of eosinophilia (> 1.0 x 10^9/L or > 10%) was increased with nintedanib compared to placebo in this study. There were no apparent increases in the incidence of immune system AEs or parasitic infections and according to the sponsor these events generally resolved with longer follow-up. It would be of interest to know whether an increased incidence of eosinophilia has been observed in previous placebo controlled studies of nintedanib.

PF-ILDs (other than IPF) are serious illnesses, and there are currently no therapies approved for their treatment. In these circumstances, the toxicity profile of nintedanib as outlined above is not unacceptable.

Clinical evaluator's recommendation

The clinical evaluator has recommended approval of Ofev/Vargatef (nintedanib) for the proposed indication and dosage regimens.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[9]

[9] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

Risk-benefit analysis

Delegate's considerations

The Delegate must make a decision under the Therapeutic Goods Act in relation to quality, safety and efficacy.

In relation to quality

The non-clinical evaluator has confirmed that there are no nonclinical objections to the new indication for the treatment of other chronic fibrosing PF-ILDs. There are no other outstanding issues. The proposed PI document is acceptable.

In relation to efficacy

No specific dose response studies have been performed. In the pivotal study, the same dose as approved for IPF was used (that is a 150 mg, BID dose). Given the similarities in disease process in the IPF and PF-ILD populations, the choice is considered acceptable.

The INBUILD trial enrolled patients that exhibited a progressive fibrosing phenotype (independently from the underlying cause of their ILDs). Patients were enrolled to this study based on the predicted progression pattern rather than underlying aetiology and underlying ILD diagnoses.

In the study patients were randomised in a 1 to 1 ratio to nintedanib 150 mg BID or placebo BID. Dose reductions to 100 mg BID were allowed in case of AEs (in line with the current recommendation for IPF patients). The primary endpoint of this study was the annual rate of decline in FVC which is considered acceptable. The same primary endpoint was used in the pivotal study investigating the effect of nintedanib in the treatment of IPF. However, it is important to highlight that the annual rate of decline in FVC is only a surrogate endpoint and therefore it is considered that a positive trend in other endpoints investigating direct clinical effects.

In the study there were three main secondary endpoints – absolute change from baseline in K-BILD total score at Week 52, time to first acute ILD exacerbation or death over 52 weeks and time to death over 52 weeks. The K-BILD score is a validated health status questionnaire for ILDs and correlates highly with the St George's Respiratory Questionnaire,[10] which was included as a key secondary endpoint in the pivotal trials of IPF.

In the study there were two co-primary populations, they are overall population and the population of patients with HRCT with UIP-like fibrotic pattern only. In both these populations in patients receiving treatment with nintedanib for 52 weeks the annual rate of decline in FVC was statistically significantly lower as compared to patients receiving placebo. In the overall population the adjusted difference between the treatment groups was 106.96 mL/year (95% CI: 65.42 to 148.50; $p < 0.0001$) and in patients with UIP like fibrotic pattern-the adjusted difference between the treatment groups was 128.20 mL/year (95% CI: 70.81 to 185.59; $p < 0.0001$). Sensitivity analyses (multiple imputation approach 1, 2 and 3) support the result of the primary analysis.

The reported differences between treatment and placebo groups was similar to those observed in studies in patients with IPF (in the INPULSIS-1 trial, the INPULSIS-2 trial (pooled data) the observed difference between the treatment and placebo group was 109.9 mL).

[10] St George's Respiratory Questionnaire: A disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease.

All other endpoints studied during the trial were considered exploratory. The endpoints that were based on measurement of FVC (time to progression or death, proportion of patients with a relative decline from baseline in FVC % predicted of > 10% or > 5%, absolute change from baseline in FVC / FVC % predicted) all gave results suggesting a benefit for nintedanib over placebo. A benefit for nintedanib was not demonstrated on other clinical endpoints such as overall survival, death due to a respiratory cause, acute exacerbations, hospitalisations or diffusion capacity. There was a suggestion of a benefit for nintedanib over placebo for time to acute exacerbation or death over the whole period of the trial (HR = 0.67 (95% CI: 0.46 to 0.98)) but this endpoint was an exploratory one.

A number of patient reported outcome measures were examined in the trial. The main measure was the K-BILD score. This instrument failed to demonstrate any statistically or clinically significant differences between the two treatments. Two other instruments (the Living With Pulmonary Fibrosis Questionnaire and the Pulmonary Fibrosis – Impact On Quality Of Life Survey) suggested a possible beneficial effect for nintedanib over placebo. However, these were exploratory endpoints.

In relation to safety

The safety findings of Study 1199.247 for the 52 weeks and the whole trial data were overall consistent with the known safety profile of nintedanib in IPF.

Overall

The term ILD encompasses a large group of over 200 pulmonary disorders. While IPF is the best known PF-ILD, there is a group of patients with different underlying clinical ILD diagnoses other than IPF who develop a progressive fibrosing phenotype during the course of their disease.

The benefit of nintedanib in the proposed new patient population is a delay in disease progression, as measured by decline in FVC. The pivotal study demonstrated a statistically significant reduction compared to placebo in the rate of decline of FVC over 52 weeks. The magnitude of this benefit (106.96 mL per year compared to placebo) is similar to that observed with nintedanib in studies in subjects with IPF (109.9 mL). Sensitivity analyses support the results of the primary analysis. Findings in various subgroups were consistent with those in the overall population.

The delay in disease progression has not been shown to translate into a survival benefit. However, the study was not designed to demonstrate improved survival. However, the proportion of patients with a > 10% relative decline in FVC % predicted was 48.9% in the placebo arm and 40.7% in the nintedanib arm. The odds ratio for this endpoint suggested a benefit for nintedanib over placebo (HR = 0.70 (95% CI: 0.52 to 0.96)). For IPF subjects, a decline in FVC of this magnitude has been associated with an increased risk of mortality.

Over the whole trial, nintedanib treatment was associated with a small increase in the incidence of overall AEs. However, nintedanib treatment was not associated with an increase in the overall incidence of severe, serious or fatal AEs. The increase in the incidence of discontinuations due to AEs was modest (22.0% versus 14.5%) suggesting that toxicity in most subjects can be managed through the use of dose interruptions and/or reductions. To put this into context, chronic fibrosing ILDs with a progressive phenotype are serious and potentially life threatening diseases.

Based on the above points, the Delegate considers the benefit-risk of Ofev/Vargatef in the proposed indication, for the treatment of other chronic fibrosing ILDs with a progressive phenotype, as favourable although advice is sought from the committee regarding the specific issues raised above.

Proposed action

The Delegate has no reason to say, at this time, that the application for Ofev/Vargatef should not be approved for registration.

Advisory Committee considerations[11]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Is chronic fibrosing interstitial lung disease with a progressive phenotype a recognised clinical entity?

The ACM agreed that chronic fibrosing interstitial lung disease with progressive phenotype' is a recognised clinical entity. The ACM further noted that there are currently no therapies approved for their treatment and this treatment will benefit affected patients.

2. Is FVC an appropriate surrogate endpoint? How well does FVC correlate with exacerbations, morbidity and death in this disease?

The ACM agreed that a decrease in FVC correlates to an increase in mortality rates and that this is an appropriate marker for surrogate endpoints.

3. Does the benefit-risk profile of nintedanib appear favourable for the proposed indication?

The ACM advised that the risk benefit profile for nintedanib is favourable for the proposed indication. The ACM stated that there would be clinical benefit in using nintedanib for the proposed indication.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Treatment of other chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Ofev/Vargatef (nintedanib (as esilate)) 100 mg and 150 mg, soft capsule, blister pack, for the following extension of indications:

> *Ofev/Vargatef is also indicated for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.*

[11] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

As such, the full indications at this time were:

> *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 indicated for the treatment of idiopathic pulmonary fibrosis (IPF).*
>
> *Ofev/Vargatef is also indicated for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.*
>
> *Ofev/Vargatef is indicated for slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).*

Specific conditions of registration applying to these goods

- This approval does not impose any requirement for the submission of periodic safety update reports (PSURs;[12]). The sponsor should note that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.

Attachment 1. Product Information

The PI for Ofev approved with the submission which is described in this AusPAR 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.

[12] A **periodic safety update report (PSUR)** is a systematic review of the global safety data of an approved medicine that becomes available during a defined time period. PSURs are also referred to as periodic benefit–risk evaluation reports (PBRERs).

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