Medicines Adverse Reactions Committee

Meeting date	12/06/2025	Agenda item	3.2.3
Title	**Nintedanib and renal adverse events**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**	**Sponsor**	
Nintedanib	Ofev	Boehringer Ingelheim (NZ) Limited	
PHARMAC funding	Nintedanib is funded under Special Authority for idiopathic pulmonary fibrosis.		
Previous MARC meetings	Tumour lysis syndrome with tyrosine kinase inhibitors and monoclonal antibodies when used in cancer treatment (December 2023 meeting).		
International action	In 2018, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the risk of renal impairment/failure with nintedanib and required new warnings in section 4.4 and 4.8. In 2021, the EMA PRAC reviewed the risk of thrombotic microangiopathy with nintedanib and required a new warning in section 4.4.		
Prescriber Update	Dissecting systemic VEGF inhibitors: effects on arteries (December 2020)		
Classification	Prescription medicine		
Usage data	In 2023, there were 474 dispensings of nintedanib 100 mg capsules to 87 people. There were 1,324 dispensings of 150 mg capsules to 233 people.		
Advice sought	**The Committee is asked to advise:** • Whether the nintedanib data sheet should be updated with regard to the description of renal adverse events. If the Committee agrees that the data sheet should be updated, the Committee is asked to advise: • Whether section 4.4 should be updated to state, 'Cases of renal impairment/failure, in some cases with fatal outcome, have been reported with nintedanib use. Patients should be monitored during nintedanib therapy, with particular attention to those patients exhibiting risk factors for renal impairment/failure. In case of renal impairment/failure, therapy adjustment should be considered'. • Whether section 4.4 should be updated to state that very few cases of nephrotic range proteinuria have been seen with or without renal function impairment, and that residual proteinuria has been observed after cessation of treatment. • Whether section 4.4 should be updated to state, 'VEGF pathway inhibitors have been associated with thrombotic microangiopathy (TMA), including very few case reports for nintedanib. If laboratory or clinical findings associated with TMA occur in a patient receiving nintedanib, treatment with nintedanib should be discontinued and thorough evaluation for TMA should be completed'. • Whether section 4.8 should be updated to list renal failure as a post-market adverse reaction.		

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1 PURPOSE

Nintedanib is a receptor tyrosine kinase inhibitor (RTKI) first approved in New Zealand in 2016 for the treatment of non-small cell lung cancer (NSCLC) and idiopathic pulmonary fibrosis (IPF). In 2021, the indications were expanded to include systemic sclerosis-associated interstitial lung disease (ILD) and other chronic fibrosing ILDs.

[redacted]

The Australian, European and UK product information all describe the risk of renal failure in their product information, and Medsafe considered that the NZ data sheet should also be updated in line with the Australia product information. A request was sent to the sponsor in December 2022. The sponsor disagreed with the Medsafe position and considered no changes were required based on their review of safety data from preclinical, clinical, post-marketing and scientific literature.

This report reviews the association between nintedanib and renal failure. The Committee is asked to advise whether changes should be made to the nintedanib data sheet with regard to the risk of renal adverse events.

2 BACKGROUND

2.1 Nintedanib

2.1.1 Indications

Nintedanib (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. [1]

Nintedanib is indicated as monotherapy for idiopathic pulmonary fibrosis (IPF), other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype and for slowing pulmonary function decline in systemic sclerosis-associated interstitial lung disease (SSc-ILD). [1]

2.1.2 Mechanisms of action

Nintedanib is a small molecule tyrosine kinase inhibitor. Nintedanib inhibits the activity of vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and β) and fibroblast growth factor receptors (FGFR 1-3). It is known as a triple angiokinase inhibitor as it blocks intracellular signalling necessary for the proliferation and survival of endothelial cells, pericytes and vascular smooth muscle cells. [1]

Tumour angiogenesis is mediated by release of proangiogenic factors by tumour cells to attract host endothelial and perivascular cells in order to facilitate oxygen and nutrient supply. VEGF-2 activates several critical pathways involved in cell proliferation, migration and survival. However, resistance to VEGF inhibition may develop due to activation of alternative angiogenic pathways, including FGFs, PDGFs, placental growth factor (PlGF), and TNF-α.

FGF-2 is a potent stimulator of angiogenesis that is frequently overexpressed in tumours and correlates with poor outcomes in NSCLC. Signalling via PDGF ligands and receptors is involved in blood vessel maturation and recruitment of pericytes and has been implicated in cancer progression. In NSCLC, nintedanib therefore interferes with the formation and maintenance of the tumour vascular system via VEGFR, FGFR and PDGFR, resulting in tumour growth inhibition and tumour stasis. [1, 2]

IPF is characterised by uncontrolled proliferation and differentiation of myoblasts and fibroblasts and excessive collagen deposition in the lung interstitial and alveolar spaces. Nintedanib inhibits processes involved in the pathogenesis of fibrotic tissue remodelling via VEGFR, PDGFR and FGFR. FGF-2 stimulates proliferation of lung fibroblasts, and PDGF stimulates proliferation, migration, and survival of myofibroblasts thought to be responsible for collagen deposition in IPF. The role of VEGF in IPF is complex and not fully understood. [1-3]

2.1.3 Safety

Adverse events [1]

Gastrointestinal events (nausea, vomiting and diarrhoea) are common with nintedanib treatment and may be dose-limiting or treatment-limiting. Diarrhoea and vomiting may lead to dehydration with or without electrolyte disturbances, which may progress to renal function impairment. In addition to symptomatic treatment, dose reduction or treatment interruption may be needed. If a reduced dose cannot be tolerated, treatment should be permanently discontinued.

Elevations of liver enzymes (ALT, AST, ALP, GGT) and bilirubin were observed in clinical trials but were reversible in most cases. Severe liver injury with fatal outcome has been reported in the post-market setting. Liver enzymes should be monitored during treatment. Dose reduction, treatment interruption or permanent discontinuation may be warranted if liver function tests are abnormal.

Inhibition of VEGFR may increase the risk of hypertension, bleeding, gastrointestinal perforation, thromboembolism, aneurysms and/or artery dissections. Wound healing may be impaired. Nephrotic range proteinuria and posterior reversible encephalopathy syndrome (PRES) have been reported in the post-market setting.

Neutropenia and sepsis may occur in NSCLC treatment. Blood counts should be monitored during therapy.

Safety in special populations [1]

Nintedanib is eliminated predominantly via biliary/faecal excretion. Patients with mild hepatic impairment have increased medicine exposure and increased risk of adverse events. The safety and efficacy of nintedanib has not been studied in patients with moderate or severe hepatic impairment and treatment is not recommended in these patients.

Less than 1% of a single oral dose of nintedanib is excreted via the kidney. Starting dose adjustments are not required in mild to moderate renal impairment. Safety has not been studied in patients with severe renal impairment.

There are no overall differences in the safety profile in elderly patients.

Nintedanib is contraindicated in pregnancy due to its mechanism of action.

2.1.4 Usage

The available usage data for nintedanib is shown in Table 1.

Table 1: Nintedanib usage data

100 mg	Year	NumDisp	NumPpl	150 mg	Year	NumDsp	NumPpl
	2019	65	20		2019	431	93
	2020	143	28		2020	733	132
	2021	219	41		2021	1036	168
	2022	324	61		2022	1261	202
	2023	474	87		2023	1324	233

The Pharmaceutical Data web tool provides summary information on community pharmacy dispensings that were funded by the New Zealand Government.

NumDisps: Number of times the pharmaceutical product is dispensed from a pharmacy to the named person on all occasions including repeats (except for administrative dispensings such as owed balances) during the year.

NumPpl: Number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year (includes people who only received a repeat dispensing during the year.

Source: Health New Zealand. 2024. Pharmaceutical Data web tool version 12 September 2024 (data extracted from the Pharmaceutical Collection on 23 July 2024). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 10 April 2025).

2.2 Renal adverse events

2.2.1 VEGFR inhibition and renal injury

Two mechanisms for renal impairment/failure have been described with nintedanib treatment: hypovolaemia due to gastrointestinal adverse effects, and disruption of VEGF signalling. Diarrhoea and vomiting are common adverse events with nintedanib treatment, and consequent electrolyte abnormalities, hypovolaemia and decreased renal perfusion may lead to renal failure. Disruption of VEGF signalling is another known mechanism of renal impairment for VEGFR inhibitors. [1, 4]

The VEGF gene family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factors (PlGF). These factors bind to the receptors VEGFR-1, VEGFR-2 and VEGFR-3. The interaction of VEGF-A with VEGFR-2 is thought to be the most important in the process of angiogenesis and the maintenance of endothelial cells. A soluble form of VEGFR-1, known as sFlt-1, also circulates at low levels as a 'decoy receptor' and has an antiangiogenic effect.

VEGF-A is expressed in the kidney by podocytes and binds to receptors (VEGFR-2) on glomerular endothelial cells leading to dimerisation of the receptors and subsequent phosphorylation of tyrosine kinases in the cytoplasmic domain. This leads to downstream activation of signalling pathways such as the RAF/MAPK/ERK pathway, endothelial nitric oxide synthase (eNOS) pathway, and mammalian target of rapamycin (mTOR) pathway (Figure 1). [5]

Figure 1: VEGF-A/VEGFR-2 signalling in the kidney and medicine targets

Source: Chang H, Gustafson S and Mehta T. 2022. The Vascular Endothelial Growth Factor (VEGF) Pathway Inhibition and Associated Nephrotoxicities. In: Fernandes Nunes AC (Eds). Chronic Kidney Disease - Beyond the Basics. Rijeka: IntechOpen.

The balance of proangiogenic factors and antiangiogenic factors, including VEGF signalling, maintains the integrity of the renal capillary bed which is made up of endothelial cells, the basement membrane and podocytes. The effects of reduced VEGF signalling are demonstrated in pre-eclampsia, where increased levels of sFlt-1 and decreased VEGF and PlGF lead to glomerular capillary endotheliosis resulting in hypertension, proteinuria and renal impairment. Similarly, *Vegfa* gene knockout in mice has been shown to induce thrombotic microangiopathy (TMA). [5]

Any medicine that inhibits VEGF signalling may theoretically affect the integrity of the glomerular filtration barrier and cause proteinuria and nephrotoxicity. The mechanism in VEGF ligand inhibition (eg, by bevacizumab) is well-described and involves disruption of downstream RAF/MAPK/ERK, eNOS and mTOR pathways leading to podocyte effacement, glomerular basement membrane thickening, microthrombi, endotheliosis, and reduction in complement factors that lead to thrombotic microangiopathy and hypertension (Figure 2). [6]

Figure 2: Pathogenesis of nephrotoxicity related to anti-VEGF therapy.

Anti-VEGF drugs interfere with multiple downstream tyrosine kinase pathways responsible for maintaining glomerular and podocyte integrity. A consequence of this disruption is the development of podocyte effacement and glomerular basement membrane thickening, both leading to proteinuria. In addition, there is development of microthrombi, endotheliosis, and reduction in complement factors that lead to thrombotic microangiopathy and hypertension. Reduced fractional excretion of sodium also contributes to the hypertension.

VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; AKT-PI3: phosphoinositide-3-kinase; MAPK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; mTOR: mammalian target of rapamycin; eNO:S endothelial nitric oxide synthase; GBM: glomerular basement membrane; MCNS: minimal change nephrotic syndrome; FSGS: focal segmental glomerulosclerosis; TMA: thrombotic microangiopathy; CFH: complement factor-H.

Source: Rangaswamy et al. 2024. Ocular and systemic vascular endothelial growth factor ligand inhibitor use and nephrotoxicity: an update. International Urology and Nephrology 56(8): 2635-2644. DOI: 10.1007/s11255-024-03990-1

The mechanism may be similar for TKIs. VEGFR inhibition by TKIs has been associated with nephropathies such as minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS) and renal thrombotic microangiopathy (TMA). Several TKIs targeting VEGFR, such as sunitinib, lenvatinib and pazopanib have known renal toxicities. [7-9]

There is some evidence from animal studies that TKI-associated podocytopathies such as MCNS and FSGC might be mediated by tyrosine phosphorylation of nephrin, a slit-diaphragm protein in podocytes that is critical for maintaining integrity of the glomerular filtration barrier. For example, a knock-in murine model that blocked tyrosine phosphorylation of nephrin resulted in proteinuria and podocyte effacement. Another study of podocyte-specific overexpression of $Vegfa_{164}$ in transgenic mice suggested that when VEGF-A availability increases, VEGFR-2 is expressed in podocytes in addition to endothelial cells, and can be phosphorylated by

podocyte-derived VEGF-A. This was associated with glomerulomegaly, mesangial expansion, basement membrane thickening, and foot process effacement. [9]

A study of biopsied kidney samples from 29 patients with solid tumours after they were treated with either a TKI (sunitinib, axitinib, or sorafenib) or a direct anti-VEGF therapy (bevacizumab or VEGF trap) found that TKIs were mostly associated with MCNS/FSGC, although two patients treated with sunitinib had TMA. Molecular imaging of TKI-induced MCD/FSGS lesions were associated with increased glomerular C-Maf–inducing protein (c-mip) expression. Bevacizumab-induced TMA was associated with upregulated glomerular RelA, reflecting increased NF-κB activity. [9, 10]

2.2.2 Proteinuria and nephrotic syndrome

Proteinuria is defined as the presence of protein in the urine. When the kidney is functioning normally, less than 150 mg of protein is excreted in the urine per day, of which around 20 mg is albumin. Mild, transient proteinuria may be caused by intense exercise, standing for long periods, pregnancy, urinary tract infection, acute febrile illness or congestive heart failure. [11]

Persistent proteinuria is a marker for kidney injury and is confirmed by two positive dipstick urine tests in a period of one to two weeks without suspected transient cause. Proteinuria is quantified by albumin:creatinine ratio (ACR) or protein:creatinine ratio (PCR). Causes of persistent proteinuria are shown in Table 2. [11]

Table 2: Causes of proteinuria

Source: bpacnz. 2013. Interpreting urine dipstick tests in adults: a reference guide for primary care June 2013. URL: https://bpac.org.nz/bt/2013/june/urine-tests.aspx (accessed 22 May 2025).

Proteinuria of greater than 3 g protein in 24 hours is referred to as nephrotic range proteinuria. Nephrotic syndrome is defined by ACR greater than 250 mg/mmol or PCR greater than 300 mg/mmol, serum albumin less than 25 g/L and oedema. Nephrotic syndrome can be caused by MCNS, FSGC, membranous nephropathy or hereditary nephropathies, or can be secondary to systemic illnesses such as diabetes and systemic lupus erythematosus. Consequences of nephrotic syndrome include infection/sepsis, hyperlipidaemia and atherosclerosis, hypocalcaemia and bone abnormalities, hypercoagulability and hypovolaemia. [12]

2.2.3 Renal thrombotic microangiopathy

Thrombotic microangiopathy (TMA) is generally characterised by microangiopathic haemolytic anaemia (MAHA), thrombocytopenia, and ischemic organ injury frequently involving the kidney. However, systemic MAHA and thrombocytopenia are not required for a diagnosis of TMA and renal-limited forms may be seen more often in the context of medicine-induced TMA. [13]

The clinical manifestations of renal TMA are haematuria, proteinuria, hypertension and renal failure. Management of medicine-induced TMA involves discontinuation of the causative medicine and supportive care. TMA is often reversible upon stopping the causative medicine, but kidney injury may persist. [8, 13]

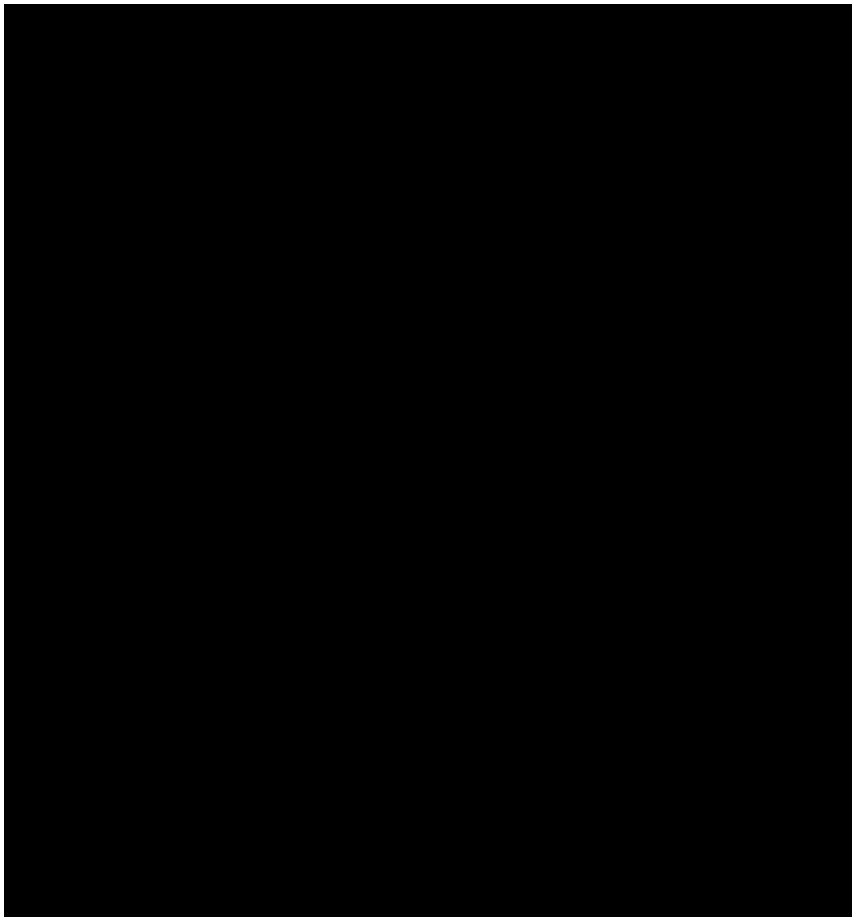
The histological changes that are diagnostic of renal TMA are glomerular thrombi (which may be missing with limited sampling) and the presence of arterial intimal oedema (mucoid/myxoid change) or fibrin. Glomerular endotheliosis, mesangiolysis and red blood cell fragments may be seen. Chronic lesions feature glomerular capillary wall double contouring. In general, certain histologic changes are not specific for any aetiology. However, it has been reported that anti-VEGF (monoclonal antibody) medicines produce a characteristic appearance of marked segmental subendothelial expansion with loose and dense hyalinosis. [13]

The pathophysiology of TMA involves endothelial injury, followed by activation of the coagulation system. Reduced eNOS expression may contribute to the development of TMA, as vascular nitric acid promotes vasodilation and reduces the risk of thrombus formation. VEGF modulates eNOS expression and therefore reduced VEGF may precipitate TMA. [13]

2.2.4 Acute renal impairment/failure

Acute renal impairment or failure is also known as acute kidney injury (AKI), and refers to a sudden decline in kidney function leading to a rise in serum creatinine and/or a fall in urine output. Renal impairment/failure is not a single condition but part of a diverse collection of syndromes, including cardiorenal syndrome, hepatorenal syndrome and sepsis. AKI may develop as a consequence of multiple interacting conditions (Figure 3). [14]

Figure 3: The clinical spectrum of acute kidney injury syndrome



AKI syndrome can develop as a consequence of different pathological conditions that might or might not lead to AKI depending on the balance between patient susceptibility and intensity of the exposure. Different pathological conditions can also interfere in a combined causality as described by the overlapping of the different circles. The dimension of the circles and the area in common with the AKI circle describe the size of the problem and the frequency of AKI for each pathological condition (in rough approximation based on data compiled from various sources). Source: Ronco C, Bellomo R and Kellum JA. 2019. Acute kidney injury. The Lancet 394(10212): 1949-1964. DOI: 10.1016/S0140-6736(19)32563-2 (accessed 17 April 2025).

The causes of AKI have traditionally been classified as prerenal, renal or postrenal. Prerenal AKI is due to decreased renal perfusion, for example due to dehydration, where prolonged hypoperfusion can result in ischaemic injury. Renal causes of AKI are disorders affecting the blood vessels, glomeruli, tubules, or interstitium. [15] The mechanisms of VEGFR inhibitor-associated nephrotoxicity are discussed in section 2.2.1. Postrenal causes of AKI involve urine outflow obstruction and are not known to be associated with nintedanib therapy.

The Kidney Disease: Improving Global Outcomes (KDIGO) defines AKI as any of the following:

- Increase in serum creatinine by ≥26 micromol/L (≥0.3 mg/dL) within 48 hours; or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 mL/kg/hour for 6 hours. [15]

The initial symptoms of AKI are weight gain and peripheral oedema. As nitrogenous products accumulate, symptoms of uraemia may occur, such as anorexia, nausea, vomiting, weakness, myoclonic jerks, seizures, confusion and coma. Asterixis and hyperreflexia may be present. Uraemic pericarditis may result in chest pain, pericardial rub or pericardial tamponade. Pleural effusion may cause dyspnoea and crackles on auscultation. [15]

Treatment involves addressing the underlying cause, which may include treating hypovolaemia and electrolyte imbalances, or stopping nephrotoxic medicines, and supportive care. Life-threatening complications of AKI may necessitate dialysis. [15]

2.3 Data sheets

The information describing renal adverse effects in local and international product information for nintedanib is summarised in table 3.

The New Zealand data sheet mentions the risk of renal failure may be a consequence of dehydration in section 4.4. The Australian and EU product information include a more detailed section on the risk of renal impairment/failure, and state that fatal cases have been reported. Monitoring and consideration of therapy adjustment are recommended.

Renal failure is a listed adverse event in section 4.8 in the Australian and EU product information, but not in the New Zealand data sheet.

The New Zealand data sheet describes the risk of nephrotic range proteinuria and states that this is reversible upon discontinuation. However, the EU SmPC and US FDA PI state that there have been cases with residual proteinuria after cessation of treatment. The NZ data sheet notes that histological findings of glomerular microangiopathy have been observed, while the Australian and EU information include a more detailed warning on TMA, stating that any clinical findings associated with thrombotic microangiopathy should be thoroughly evaluated and treatment with nintedanib should be discontinued.

Table 3: Information on the risk of renal failure with nintedanib in New Zealand and international product information for nintedanib (Ofev)

New Zealand	Australia	EU and UK	US	Canada
Section 4.4 Special warnings and precautions for use				
NSCLC section. Similar text for IPF. **Nausea and vomiting** Nausea and vomiting, mostly of mild to moderate severity, were frequently reported GI adverse events. If symptoms persist despite appropriate supportive care (including antiemetic therapy), dose reduction, treatment interruption, or discontinuation of therapy with OFEV may be required. Diarrhoea and vomiting may lead to dehydration with or without electrolyte disturbances **which may progress to renal function impairment.** In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored if relevant GI adverse events occur.	*Same text as NZ regarding nausea and vomiting.* **Renal function** Cases of renal impairment/failure, in some cases with fatal outcome, have been reported with nintedanib use (see section 4.8 Adverse effects). Patients should be monitored during nintedanib therapy, with particular attention to those patients exhibiting risk factors for renal impairment/failure. In case of renal impairment/failure, therapy adjustment should be considered.	*The nausea and vomiting section does not mention progression to renal failure.* **Renal function** Cases of renal impairment/failure, in some cases with fatal outcome, have been reported with nintedanib use. Patients should be monitored during nintedanib therapy, with particular attention to those patients exhibiting risk factors for renal impairment/failure. In case of renal impairment/failure, therapy adjustment should be considered. *Note: In the EU, Ofev is indicated for IPF, other chronic fibrosing ILDs and SSc-ILD, but not NSCLC. Another product, Vargatef, is indicated for NSCLC. The Vargatef EU SmPC also includes the above text.*	*The nausea and vomiting section does not mention progression to renal failure.*	*Same text as NZ regarding nausea and vomiting.*

New Zealand	Australia	EU and UK	US	Canada
Nephrotic range proteinuria Very few cases of nephrotic range proteinuria have been reported post-marketing. Histological findings in individual cases were consistent with glomerular microangiopathy with or without renal thrombi. Reversal of symptoms has been observed after OFEV was discontinued. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome.	*Same text as NZ.*	**Nephrotic range proteinuria and thrombotic microangiopathy** Very few cases of nephrotic range proteinuria with or without renal function impairment have been reported post-marketing. Histological findings in individual cases were consistent with glomerular microangiopathy with or without renal thrombi. Reversal of the symptoms has been observed after Ofev was discontinued, with residual proteinuria in some cases. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome. VEGF pathway inhibitors have been associated with thrombotic microangiopathy (TMA), including very few case reports for nintedanib. If laboratory or clinical findings associated with TMA occur in a patient receiving nintedanib, treatment with nintedanib should be discontinued and thorough evaluation for TMA should be completed. *Note: The Vargatef EU SmPC includes the same text as NZ*	**Nephrotic range proteinuria** Cases of proteinuria within the nephrotic range have been reported in the post-marketing period. Histological findings, when available, were consistent with glomerular microangiopathy with or without renal thrombi. Improvement in proteinuria has been observed after OFEV was discontinued; however, in some cases, residual proteinuria persisted. Consider treatment interruption in patients who develop new or worsening proteinuria.	*Same text as NZ.*

New Zealand	Australia	EU and UK	US	Canada
Section 4.8 Undesirable effects				
Proteinuria NSCLC: common IPF: uncommon Other ILDs: uncommon SSc-ILD: Not known	*Same as NZ.* Post-marketing experience **Renal failure** – frequency unknown	**Renal failure** IPF: Not known Other ILDs: Not unknown SSc-ILD: Uncommon **Proteinuria** IPF: Uncommon Other ILDs: Uncommon SSc-ILD: Not known In clinical trials, the frequency of patients who experienced proteinuria was low and comparable between the treatment arms (Ofev 0.8% versus placebo 0.5% for INPULSIS; Ofev 1.5% versus placebo 1.8% for INBUILD; Ofev 1.0% versus placebo 0.0% for SENSCIS). Nephrotic syndrome has not been reported in clinical trials. *Text from section 4.4 on nephrotic range proteinuria repeated here.* *The Vargatef EU SmPC (indicated for NSCLC) lists renal failure as an uncommon ADR and proteinuria as a common ADR.*	Post-marketing experience **Proteinuria**	Post-marketing experience **Proteinuria**

3 SCIENTIFIC INFORMATION

3.1 Literature case reports

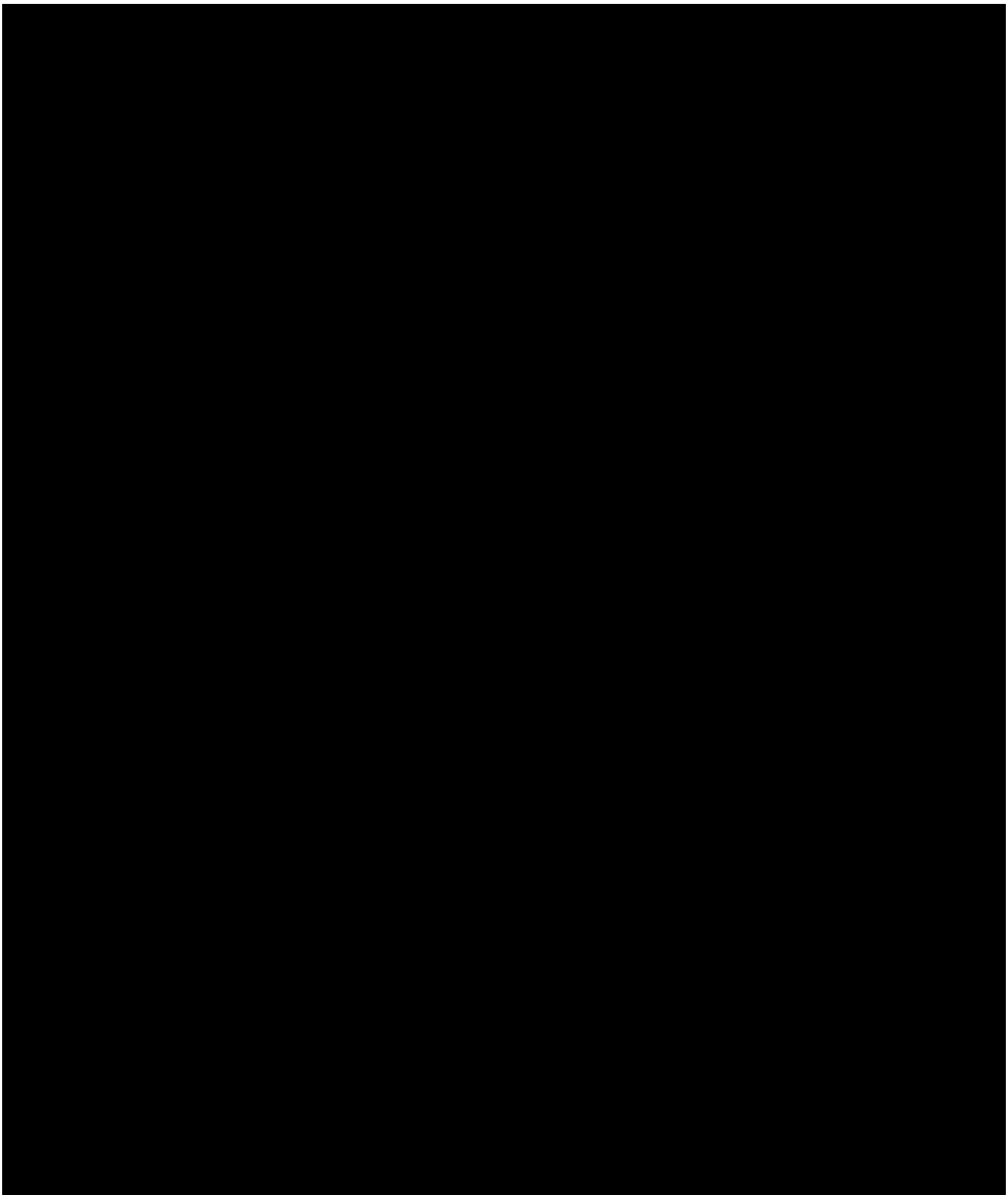
Table 4: Summary of literature case reports describing renal injury with nintedanib

Author, year of publication (country)	Age, sex, indication	Title and summary
Fujita et al, 2021 (Japan) [16]	83 M IPF	**Nintedanib-induced renal thrombotic microangiopathy** During the first months of nintedanib therapy at 150 mg twice daily, the patient developed proteinuria, diarrhoea, anorexia and decreasing serum albumin. After nine months, the dose was reduced to 100 mg twice daily. One month later, the urine protein/creatinine (Cr) ratio was 7.90 g/g Cr (normal range: <0.15 g/g Cr). Subsequent ratios were approximately 2 g/g Cr. Concomitant medicines included doxazosin, nifedipine, telmisartan, bisoprolol, furosemide and trichlormethiazide. A percutaneous renal biopsy revealed typical thrombotic microangiopathy (TMA) findings such as microaneurysms filled with pale material, segmental double contours of glomerular basement membranes, and intracapillary foam cells. Direct immunofluorescence identified non-specific deposits of immunoglobulin (Ig) A, IgM, and C1q, and no deposit of IgG and C3. Electron microscopy revealed microaneurysmal dilatation of a capillary loop with marked widening of the subendothelial spaces. The findings strongly indicated nintedanib-induced TMA and treatment was discontinued. Although the nephrotic syndrome recovered within 1 year, the renal dysfunction persisted.
Hasegawa et al, 2020 (Japan) [17]	68 M IPF	**Nintedanib-induced glomerular microangiopathy: a case report** The patient had a history of a history of primary aldosteronism, idiopathic pulmonary fibrosis, and pleomorphic carcinoma of the lung and developed severe proteinuria and leg oedema. He was a heavy smoker. After partial lung resection he had been treated with nintedanib (300 mg/day) to halt the progression of pulmonary fibrosis for 10 months. Concomitant medicines included eplerenone and amlodipine. Four months prior to the initiation of nintedanib, his serum creatinine was 0.78 mg/dL and neither haematuria nor proteinuria was evident. One week after nintedanib initiation, dipstick urine showed proteinuria and haematuria, and he complained of nausea and diarrhoea, which was controlled by symptomatic treatment. In addition, his blood pressure increased, so the dose of eplerenone was increased. Initial laboratory tests showed hypoalbuminemia (2.5 g/dL) and proteinuria (protein-to creatinine ratio: 4.1 g/g Cr), leading to a diagnosis of nephrotic syndrome. Kidney biopsy at 10 months after the onset of proteinuria showed prominent endothelial and mesangial injury. Proteinuria and haematuria improved after nintedanib withdrawal, with no recurrence during two years of follow up.

Author, year of publication (country)	Age, sex, indication	Title and summary
Inoue et al, 2020 (Japan) [18]	45 M IPF	**Renal thrombotic microangiopathy during nintedanib treatment for idiopathic pulmonary fibrosis** A 45-year-old male was referred to a nephrology clinic with isolated proteinuria while taking nintedanib and prednisolone for IPF. One year after initiation of nintedanib, a urine dipstick test was positive for protein. The proteinuria gradually increased, with a protein to creatinine ratio of 1.3 g/g Cr at the time of referral, three years after beginning treatment. His serum creatinine level was 0.70 mg/dL and his haematuria result was negative. There was no personal or family history of renal disease. A kidney biopsy showed extensive widening of the subendothelial space of the glomerular capillaries and focal glomerular capillary thrombosis. Immunofluorescent staining results were unremarkable except for capillary IgM deposition. Transmission electron micrographs showed subendothelial widening with duplication of capillary basement membranes. A diagnosis of renal thrombotic microangiopathy was made. Nintedanib was suspected to be the cause of TMA, however discontinuation was not practical due to worsening respiratory symptoms. Six months later, the patient received a lung transplant and nintedanib was discontinued. Proteinuria was resolved one month after transplantation. The authors commented that contribution of post-transplant immunosuppression to the resolution of proteinuria cannot be ruled out, but considered this unlikely.
Ismail et al, 2017 (Australia) [19]	59 F IPF	**Anti-glomerular basement membrane glomerulonephritis following nintedanib for idiopathic pulmonary fibrosis: a case report** A 59-year-old Caucasian woman experienced a 4-week history of painless haematuria and increasing lethargy associated with acute kidney injury (AKI). She had been diagnosed with IPF four years earlier and had been taking nintedanib for 4 months. Treatment was complicated by diarrhoea that required a dose reduction. Her other comorbidities include a history of breast cancer in remission, Barrett's oesophagus, and osteoporosis. She was an ex-smoker. There was no previous history of renal disease. The physical examination was consistent with dehydration and pulmonary fibrosis. The laboratory investigations suggested a nephritic syndrome and AKI. Biopsy showed evidence of an anti-GBM antibody associated necrotizing crescentic glomerulonephritis with linear deposition of IgG along the glomerular basement membrane, with 100% crescents (7 out of 7), with rupture of Bowman's capsule and acute tubular injury. The clinical presentation and laboratory findings were consistent with anti-GBM disease. Nintedanib was discontinued. There was a reduction in anti-GBM antibodies, and this remained within the normal range for the 12 months of follow-up.

Author, year of publication (country)	Age, sex, indication	Title and summary
Katari et al, 2024 [20]	74 F IPF	**A nintedanib dilemma** Two months after diagnosis with IPF, a 74-year-old woman was started on nintedanib 150 mg twice daily. Labs prior to initiation showed normal renal function (serum creatinine 0.88mg/dL) with no signs of proteinuria. During initiation, the patient experienced mild diarrhoea that self-resolved after a month. Three months after initiation she developed an acute kidney injury (serum creatinine 1.3). The nintedanib dose was reduced to 150 mg daily but three months later elevated creatinine persisted (serum creatinine 1.13 rising to 1.79), and new persistent proteinuria was observed (>500mg/dL). Nintedanib was withheld eight months after initiation, with resolution of the proteinuria and improvement in renal function one month later (serum creatinine 1.19).
Ouellet et al, 2025 [21]	69 M IPF	**Reversible glomerular thrombotic microangiopathy associated with nintedanib in a kidney transplant recipient** A 69-year-old man was diagnosed with IPF and received treatment with nintedanib. One year later, he received a kidney transplant after diabetic nephropathy. Immunosuppression included a basiliximab induction followed by tacrolimus, mycophenolate mofetil, and steroids as maintenance. The postoperative course was uneventful, with an eGFR of 72 ml/min/1.73 m^2. Three months after the transplant, the patient was hospitalised for a decline in renal function (creatinine: 132 mmol/l vs. 94 mmol/l) and nephrotic syndrome (albuminemia: 26 g/l and proteinuria: 1430 mg/mmol) with haematuria (30 red blood cells/mm^3). The patient had mild hypertension and pretibial oedema. The autoimmune workup was negative and there were no anti-HLA antibodies or marked cytopenia. A graft biopsy showed podocyte hyperplasia mimicking cellular crescents (25% of glomeruli) along with focal microthromboses (15% of glomeruli) and signs of endothelial activation. There was no evidence of rejection. Immunofluorescence showed polytypic IgA deposits, also present on the day-0 biopsy (likely donor-derived). The findings were consistent with glomerular thrombotic microangiopathy, which was considered secondary to nintedanib toxicity. Nintedanib was discontinued with marked improvement of albumin levels and renal function within three weeks. Proteinuria gradually decreased and was completely resolved after 7 months, with ACE inhibitors and SGLT-2 inhibitors. Treatment of IPF with pirfenidone was initiated three months later. A biopsy performed nine months after nintedanib withdrawal showed almost normal glomeruli.

[redacted]



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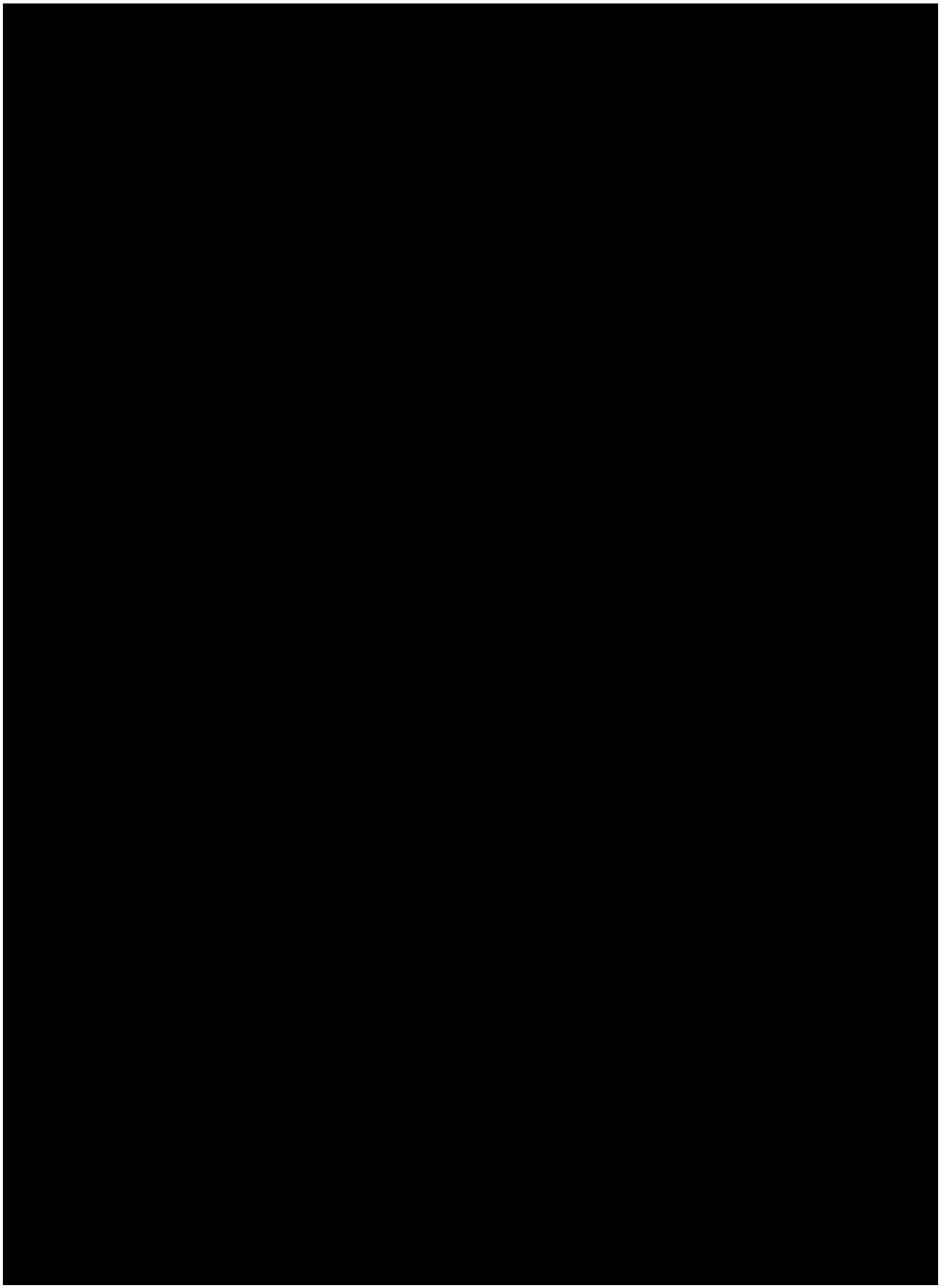

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3.3 Regulator reviews

3.3.1 Renal impairment/failure

In 2018, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) requested a cumulative review of renal impairment/failure in the context of assessment of a Periodic Safety Update Report (PSUR) for Ofev.

The sponsor identified 148 cases of acute renal failure (30 cases reported in clinical trials and 118 cases reported during post-marketing). There were 47 cases with a fatal outcome and in 11 cases renal failure was the major cause of death. A positive dechallenge was reported in 16 cases and a positive re-challenge in 2 cases.

Two possible mechanisms by which nintedanib causes renal impairment/failure were noted: a direct effect of nintedanib on the kidney through inhibition of PDGFR and VEGFR, and through diarrhoea and dehydration. It was considered that the same level of evidence (number of cases, relatedness to nintedanib in reported cases, plausible mechanism) was available for cases with and without diarrhoea, vomiting or dehydration.

Based on the high number of reported cases in which the contributing role of nintedanib could not be excluded, the plausible mechanisms, the high number of cases with fatal outcome and the seriousness of such adverse drug reaction, the PRAC concluded that renal failure should be added as a new warning in section 4.4 and as a new adverse drug reaction with a frequency 'unknown' in section 4.8 of the SmPC. [4]

In 2022, the Australian Therapeutic Goods Administration (TGA) reported that a safety update was made to the Ofev product information to include warnings on renal failure in section 4.4 and 4.8 of the product information. [22]

3.3.2 Thrombotic microangiopathy

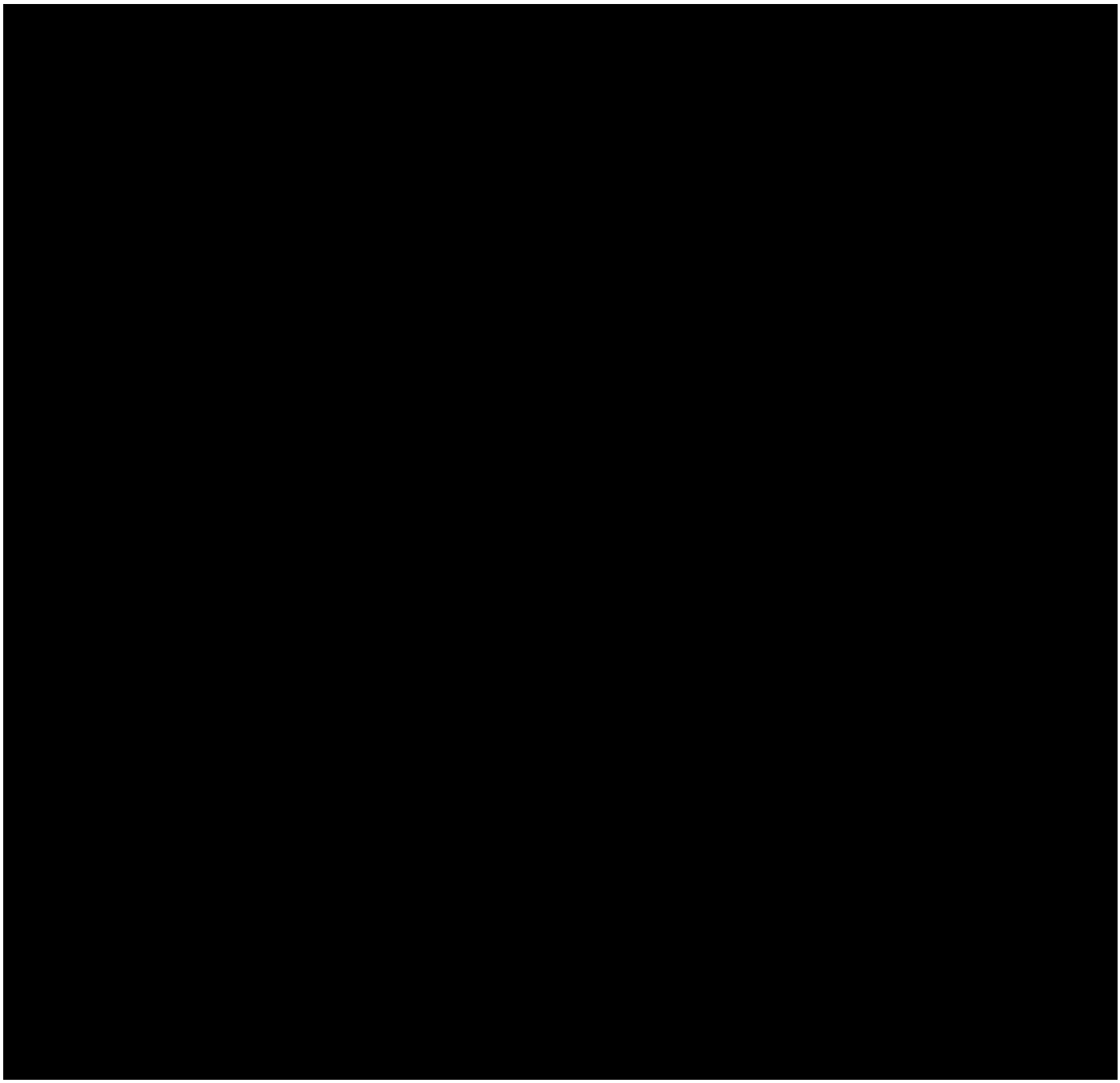
In 2021, the EMA PRAC reviewed the risk of thrombotic microangiopathy and considered that in view of available data on thrombotic microangiopathy from the literature, spontaneous reports, and a plausible mechanism of action and potential class effect, a causal relationship between nintedanib and thrombotic

microangiopathy could not be excluded. The PRAC concluded that the nintedanib product information (respiratory indication) should be amended accordingly. [23]

3.4 Spontaneous case reports

3.4.1 New Zealand

There have been five case reports where nintedanib was a suspect medicine. None of the reports describe renal adverse events.



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4 DISCUSSION AND CONCLUSIONS

Nintedanib may cause renal failure both through hypovolaemia and direct effects on the kidney due to VEGF inhibition. Renal adverse events are described as a class effect of VEGF and VEGFR inhibition in the literature. Several TKIs targeting VEGFR, such as sunitinib, lenvatinib and pazopanib, describe renal toxicity in their product information.

The risk of renal impairment/failure is currently characterised in the New Zealand data sheet as a possible consequence of dehydration. The data sheet also describes the risk of nephrotic range proteinuria with histological findings of glomerular microangiopathy. However, the European SmPC, UK SPC and Australian product information include a dedicated warning on renal function impairment in section 4.4 and list renal failure as an ADR in section 4.8.

The risk of renal impairment has been assessed by the EMA PRAC with resulting changes to the EU SmPC. The EMA PRAC considered that a similar level of evidence is available for renal impairment with and without diarrhoea, vomiting or dehydration. The EU SmPC was updated to describe renal impairment/failure as a potentially fatal adverse event that should be monitored, with consideration of treatment modification. Renal failure was also added to section 4.8 Undesirable effects. Similar updates to the Australian product information were undertaken.

The EMA PRAC also reviewed the risk of thrombotic microangiopathy and considered that a causal relationship could not be excluded, on the basis of literature and spontaneous reports, a plausible mechanism of action and potential class effect. Compared to the NZ data sheet, the EU SmPC and UK SPC include additional information of this risk. They state that proteinuria may persist and include a warning stating that VEGF pathway inhibitors, including nintedanib, have been associated with TMA and to discontinue treatment if TMA occurs.

The literature search identified five published case reports describing proteinuria and renal impairment during nintedanib treatment. In three cases, renal biopsy was consistent with thrombotic microangiopathy and in one case biopsy was not carried out. In one case, renal injury was due to anti-GBM antibodies.

There have been no case reports of renal adverse effects with nintedanib reported to Medsafe. However, a large number of post-market cases of renal failure were identified in both the 2018 EMA PRAC review [redacted]

The Committee is asked to advise whether the nintedanib data sheet should be updated with regard to the description of renal adverse events.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the nintedanib data sheet should be updated with regard to the description of renal adverse events.

If the Committee agrees that the data sheet should be updated, the Committee is asked to advise:

- Whether section 4.4 should be updated to state, 'Cases of renal impairment/failure, in some cases with fatal outcome, have been reported with nintedanib use. Patients should be monitored during nintedanib therapy, with particular attention to those patients exhibiting risk factors for renal impairment/failure. In case of renal impairment/failure, therapy adjustment should be considered'.
- Whether section 4.4 should be updated to state that very few cases of nephrotic range proteinuria have been seen with or without renal function impairment, and that residual proteinuria has been observed after cessation of treatment.
- Whether section 4.4 should be updated to state, 'VEGF pathway inhibitors have been associated with thrombotic microangiopathy (TMA), including very few case reports for nintedanib. If laboratory or clinical findings associated with TMA occur in a patient receiving nintedanib, treatment with nintedanib should be discontinued and thorough evaluation for TMA should be completed'.
- Whether section 4.8 should be updated to list renal failure as a post-market adverse reaction.

[redacted]

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