NEW ZEALAND DATA SHEET - FOTIVDA®
(TIVOZANIB HYDROCHLORIDE MONOHYDRATE)

1. PRODUCT NAME

Fotivda 890 microgram hard capsules
Fotivda 1340 microgram hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fotivda 890 microgram hard capsules
Each hard capsule contains tivozanib hydrochloride monohydrate equivalent to 890 microgram tivozanib.

Excipients with known effect
Each hard capsule contains trace amounts of tartrazine (E102) (8 12% of the yellow printing ink composition) (see section 4.4).

Fotivda 1340 microgram hard capsules
Each hard capsule contains tivozanib hydrochloride monohydrate equivalent to 1340 microgram tivozanib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Fotivda 890 microgram hard capsules
Hard capsule with dark blue opaque cap and bright yellow opaque body, printed with yellow ink “TIVZ” on the cap and with dark blue ink “LD” on the body.

Fotivda 1340 microgram hard capsules
Hard capsule with bright yellow opaque cap and bright yellow opaque body, printed with dark blue ink “TIVZ” on the cap and with dark blue ink “SD” on the body.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Fotivda is indicated for the first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC.

4.2 DOSE AND METHOD OF ADMINISTRATION

Fotivda should be supervised by a physician experienced in the use of anticancer therapies.

DOSE
The recommended dose of tivozanib is 1340 microgram once daily for 21 days, followed by a 7 day rest period to comprise one complete treatment cycle of 4 weeks.

This treatment schedule should be continued until disease progression or unacceptable toxicity.

No more than one dose of Fotivda must be taken per day.

Dose modification
The occurrence of undesirable effects may require temporary interruption and/or dose reduction of tivozanib therapy (see section 4.4). In the pivotal study, the dose was reduced for grade 3 events and interrupted for grade 4 events.

When dose reduction is necessary, the tivozanib dose can be reduced to 890 microgram once daily with the normal treatment schedule of 21 days of dosing, followed by a 7 day rest period.

Missed dose
In the case of a missed dose a replacement dose must not be taken to make up for a forgotten dose. The next dose should be taken at the next scheduled time.

In the case of vomiting a replacement dose should not be taken; the next dose should be taken at the next scheduled time.

Special populations
Paediatric population
The safety and efficacy of tivozanib in children and adolescents aged below 18 years have not been established. No data are available. There is no relevant use of tivozanib in the paediatric population in the indication advanced renal cell carcinoma.

Elderly patients
No dose adjustment is required in patients 65 years of age or older (see sections 4.4 and 5.1).

Patients with renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Caution is advised in patients with severe renal impairment due to limited experience and in patients undergoing dialysis as there is no experience of tivozanib in this patient population.

Patients with hepatic impairment
All patients should have liver function tests evaluated, including aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase (AP), to determine hepatic function before starting and during treatment with tivozanib.

Tivozanib is not recommended in patients with severe hepatic impairment. Patients with moderate hepatic impairment should only be treated with one tivozanib 1340 microgram capsule every other day as they may be at an increased risk of adverse reactions due to increased exposure with the dose of 1340 microgram every day (see section 4.4 and section 5.2). No dose adjustment is required when administering tivozanib to patients with mild hepatic impairment. Tivozanib should be used with caution in patients with mild and moderate hepatic impairment with close monitoring of tolerability.

METHOD OF ADMNISTRATION
Fotivda is for oral use.

Fotivda may be taken with or without food (see section 5.2). The capsules must be swallowed whole with a glass of water and must not be opened.

4.3 CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co administration with herbal preparations containing St. John’s wort (Hypericum perforatum) (see section 4.5).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypertension

In clinical studies with tivozanib, hypertension (including persistent severe hypertension) has occurred (see section 4.8). In approximately one third of the patients, hypertension developed within the first 2 months of treatment. Blood pressure should be well controlled prior to initiating tivozanib. During treatment, patients should be monitored for hypertension and treated as needed with anti hypertensive therapy according to standard medical practice. In the case of persistent hypertension despite use of anti hypertensive therapy, the tivozanib dose should be reduced, or the treatment interrupted and re initiated at a lower dose once the blood pressure is controlled, according to clinical judgment (see section 4.2). Discontinuation of treatment should be considered in cases of persistent severe hypertension, posterior reversible encephalopathy syndrome (see below), or other complications of hypertension. Patients receiving anti hypertensive medication should still be monitored for hypotension when tivozanib is either interrupted or discontinued.

Arterial thromboembolic events

In clinical studies with tivozanib, arterial thromboembolic events (ATEs) have occurred (see section 4.8). Risk factors for ATE include malignant disease, age > 65 years, hypertension, diabetes mellitus, smoking, hypercholesterolaemia, and prior thromboembolic disease. Tivozanib has not been studied in patients who had an ATE within the preceding 6 months of clinical study initiation. Tivozanib must be used with caution in patients who are at risk for, or who have a history of these events (such as myocardial infarction, stroke).

Venous thromboembolic events

In clinical studies with tivozanib, venous thromboembolic events (VTEs) have been reported including pulmonary embolism and deep vein thrombosis (see section 4.8). Risk factors for VTEs include major surgery, multiple trauma, prior VTEs, advanced age, obesity, cardiac or respiratory failure, and prolonged immobility. Tivozanib has not been studied in patients who had a VTE within the preceding 6 months of clinical study initiation. Treatment decision, especially in patients who are at risk for VTEs, should be based on individual patient benefit/risk assessment.

Cardiac failure

In clinical studies with tivozanib as monotherapy for the treatment of patients with RCC, cardiac failure has been reported (see section 4.8). Signs or symptoms of cardiac failure should be periodically monitored throughout treatment with tivozanib. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of tivozanib therapy, plus treatment of potential underlying causes of cardiac failure e.g. hypertension.

Haemorrhage

In clinical studies with tivozanib, haemorrhagic events have been reported (see section 4.8). Tivozanib must be used with caution in patients who are at risk for, or who have a history of bleeding. If any bleeding requires medical intervention, tivozanib should be temporarily interrupted.

Proteinuria

Proteinuria has been reported in clinical studies with tivozanib (see section 4.8). Monitoring for proteinuria before initiation of, and periodically throughout treatment is recommended. For patients who develop Grade 2 (> 1.0-3.4 g/24 hours) or Grade 3 (≥ 3.5 g/24 hours) proteinuria (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]), the dose of tivozanib has to be reduced or the treatment temporarily interrupted. If the patient develops Grade 4 proteinuria (nephrotic syndrome) tivozanib has to be discontinued. Risk factors for proteinuria include high blood pressure.

Hepatotoxicity

In clinical studies with tivozanib, elevations of ALT, AST, and bilirubin have been reported (see section 4.8). The majority of AST and ALT elevations were not accompanied with concomitant elevations of bilirubin. AST, ALT, bilirubin, and AP should be monitored before initiation of and periodically throughout treatment with tivozanib because of the potential risk of hepatotoxicity (see section 4.2).

Tivozanib is not recommended in patients with severe hepatic impairment. Patients with moderate hepatic impairment should only be treated with one tivozanib 1340 microgram capsule every other day as they may be at an increased risk of adverse reactions due to increased exposure with the dose of 1340 microgram every day (see section 5.2). No dose adjustment is required when administering tivozanib to patients with mild hepatic impairment. Tivozanib should be used with caution in patients with mild and moderate hepatic impairment with close monitoring of tolerability.

Posterior reversible encephalopathy syndrome
In clinical studies, one case of posterior reversible encephalopathy syndrome (PRES) was confirmed after treatment with tivozanib (see section 4.8). PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic Resonance Imaging is necessary to confirm the diagnosis of PRES. Tivozanib must be discontinued in patients developing signs or symptoms of PRES. The safety of re initiating tivozanib therapy in patients previously experiencing PRES is not known and tivozanib should only be used with caution in these patients.

Hand foot skin reaction
In clinical studies with tivozanib, hand foot skin reaction (palmar-plantar erythrodysaesthesia) has been reported. Most events in the five renal cell carcinoma monotherapy studies were CTC Grade 1 or 2 (≥ CTC Grade 3 was observed in < 2% of patients treated with tivozanib) and there were no serious events (see section 4.8). Management of patients experiencing HFSR may include topical therapies for symptomatic relief with consideration of temporary interruption and/or reduction in treatment dose or, in severe or persistent cases, permanent discontinuation of treatment.

QT interval prolongation
In clinical studies with tivozanib, QT/QTc interval prolongation has been reported (see section 4.8 and section 5.1). QT/QTc interval prolongation may lead to an increased risk for ventricular arrhythmias. It is recommended that tivozanib be used with caution in patients with a history of QT interval prolongation or other relevant pre existing cardiac disease and those receiving other medications known to increase the QT interval. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within the normal range is recommended.

Gastrointestinal perforation/fistula
It is recommended that symptoms of gastrointestinal perforation or fistula should be periodically monitored throughout treatment with tivozanib and that tivozanib should be used with caution in patients at risk for GI perforation or fistula.

Wound healing complications
For precautionary reasons, temporary interruption of tivozanib therapy is recommended in patients undergoing major surgical procedures. The decision to resume tivozanib therapy after surgery should be based on clinical judgment of adequate wound healing.

Hypothyroidism
In clinical studies with tivozanib, hypothyroidism has been reported (see section 4.8). Hypothyroidism has been observed to occur at any time during treatment with tivozanib, developing as early as within two months of treatment initiation. Risk factors for hypothyroidism include prior history of hypothyroidism and use of anti thyroid medications. Thyroid function should be monitored before initiation of, and periodically throughout treatment with tivozanib. Hypothyroidism should be treated according to standard medical practice.

Tartrazine
Fotivda 890 microgram hard capsules contain tartrazine (E102) which may cause allergic reactions.

Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Fotivda, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm

Elderly patients
Dysphonia, diarrhoea, fatigue, weight decreased, appetite decreased and hypothyroidism occurred more commonly in patients ≥ 65 years of age. Healthcare professions should be aware that elderly patients may be at increased risk of adverse reactions.

Paediatric population
The safety and efficacy of tivozanib in children and adolescents aged below 18 years have not been established. No data are available. There is no relevant use of tivozanib in the paediatric population in the indication advanced renal cell carcinoma.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Contraindication of concomitant use
Herbal preparations containing St. John's wort (Hypericum perforatum) are contraindicated. If a patient is already taking St John's wort, this should be stopped before starting tivozanib treatment. The inducing effect of St John's wort may persist for at least 2 weeks after cessation of treatment with St John's wort (see section 4.3).

Strong CYP3A4 inducers
In a clinical study in healthy volunteers, co administration of a single 1340 microgram dose of tivozanib with a strong CYP3A4 inducer at steady state (rifampin 600 mg once daily) decreased the average half-life of tivozanib from 121 to 54 hours which was associated with a decrease in the single dose $AUC_{0-\infty}$ of 48% compared with $AUC_{0-\infty}$ in the absence of rifampin. Average C_{max} and AUC_{0-24hr} were not significantly affected (8% increase and 6% decrease respectively). The clinical effects of strong CYP3A4 inducers on repeated daily dosing of tivozanib has not been studied but potentially the average time to reach steady state and the average steady state serum concentration of tivozanib may be reduced, due to the reduction in half life. It is recommended that concomitant administration of tivozanib with strong CYP3A4 inducers, if used, should be undertaken with caution.

Moderate CYP3A4 inducers are not expected to have a clinically relevant effect on tivozanib exposure.

CYP3A4 inhibitors
In a clinical study in healthy volunteers, co administration of tivozanib with a potent CYP3A4 inhibitor, ketoconazole (400 mg once daily), had no influence on tivozanib serum concentrations (C_{max} or AUC); therefore, tivozanib exposure is unlikely to be altered by CYP3A4 inhibitors.

Medicinal products for which intestinal absorption is restricted by BCRP
Tivozanib inhibits the transporter protein BCRP *in vitro*, but the clinical relevance of this finding is unknown (see section 5.2). Caution should be exercised if tivozanib is co-administered with rosuvastatin. Alternatively, a statin not subject to restriction of intestinal absorption by BCRP should be considered. Patients taking an oral BCRP substrate with a clinically-relevant efflux interaction in the gut should ensure that a suitable time window (e.g. 2 hours) is applied between administration of tivozanib and the BCRP substrate.

Contraceptives
It is currently unknown whether tivozanib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method (see section 4.6).

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential/contraception in males and females
Women of childbearing potential should avoid becoming pregnant while on tivozanib. Female partners of male patients taking tivozanib should also avoid pregnancy. Effective methods of contraception should be used by male

and female patients and their partners during therapy, and for at least one month after completing therapy. It is currently unknown whether tivozanib may reduce the effectiveness of hormonal contraceptives and therefore women using hormonal contraceptives should add a barrier method.

Pregnancy
There are no data from the use of tivozanib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Tivozanib should not be used during pregnancy. If tivozanib is used during pregnancy, or if the patient becomes pregnant while receiving tivozanib, the potential hazard to the foetus must be explained to the patient.

Breast-feeding
It is unknown whether tivozanib is excreted in human milk, but the potential exists. Because of the potential for tivozanib mediated adverse reactions in breastfed infants, women should not breast-feed while taking tivozanib.

Fertility
Animal studies indicate that male and female fertility may be affected by treatment with tivozanib (see section 5.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tivozanib may have a minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience asthenia, fatigue, and/or dizziness during treatment with tivozanib (see section 4.8).

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile
Pooled data of 674 patients with advanced RCC who continued to receive tivozanib as their initial on trial therapy in the five core RCC monotherapy studies have been evaluated in the overall assessment of safety and tolerability of tivozanib.

The most important serious adverse reaction is hypertension.

The most common adverse reactions of any grade include hypertension (47.6%), dysphonia (26.9%), fatigue (25.8%) and diarrhoea (25.5%).

In the five core RCC monotherapy studies tivozanib was discontinued in a total of 20 patients (3%) owing to adverse reactions, most commonly due to hypertension (0.4%), persistent severe hypertension (0.3%), or acute myocardial infarction (0.3%). The most frequent adverse reactions leading to tivozanib dose reduction/ interruption were hypertension (4.7%), diarrhoea (3.1%), fatigue (1.8%).

In patients receiving tivozanib as initial therapy, there were three adverse reactions with outcome death; one was uncontrolled hypertension in the setting of a suspected overdose (see section 4.9) and two were reported simply as death.

Tabulated summary of adverse reactions
Adverse reactions occurring in patients who continued to receive tivozanib as their initial on trial therapy in the five RCC monotherapy studies were pooled and are listed below by MedDRA body system organ class (SOC) and frequency. Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and not known (cannot be estimated from available data). Within each SOC, adverse reactions are presented in order of decreasing seriousness.

Table 1: Tabulated list of adverse reactions (presented using frequencies for all-causality adverse events)

System Organ Class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations			Fungal infection Pustular rash		
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia Haemoglobin increased		
Endocrine disorders		Hypothyroidism	Hyperthyroidism Goitre[1]		
Metabolism and nutrition disorders	Decreased appetite	Anorexia			
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache	Peripheral neuropathy[2] Dizziness Dysgeusia[3]	Transient ischaemic attack Memory impairment[4]	Posterior reversible encephalopathy syndrome (PRES)[5]	
Eye disorders		Vision impairment[6]	Increased lacrimation		
Ear and labyrinth disorders		Vertigo Tinnitus	Ear congestion		
Cardiac disorders		Myocardial infarction (acute) / ischaemia[7] Angina pectoris Tachycardia[8]	Pulmonary oedema Coronary artery insufficiency Electrocardiogram QT prolonged		
Vascular disorders	Hypertension	Haemorrhage[9] Arterial thromboembolism[10] Venous thromboembolism[11] Persistent severe hypertension[12] Flushing[13]			Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dyspnoea[14] Dysphonia Cough	Epistaxis Rhinorrhoea Nasal congestion			
Gastrointestinal disorders	Abdominal pain[15] Nausea Diarrhoea Stomatitis[16]	Pancreatitis[17] Dysphagia[18] Vomiting Gastrooesophageal reflux disease Abdominal distension Glossitis[19] Gingivitis[20] Dyspepsia Constipation Dry mouth Flatulence	Duodenal ulcer		
Hepatobiliary disorders		ALT increased / AST increased[21] Gamma-glutamyltransferase increased Blood alkaline phosphatase increased			

System Organ Class	Very common	Common	Uncommon	Rare	Not known
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome / Hand foot skin reaction (PPE/HFS)	Skin exfoliation Erythema[22] Pruritus[23] Alopecia Rash[24] Acne[25] Dry skin	Urticaria Dermatitis[26] Hyperhidrosis Xeroderma		
Musculoskeletal and connective tissue disorders	Back pain	Arthralgia Myalgia Musculoskeletal chest pain	Muscular weakness		
Renal and urinary disorders		Proteinuria Blood creatinine increased			
General disorders and administration site conditions	Pain[27] Asthenia Fatigue	Chest pain[28] Chills[29] Pyrexia Peripheral oedema	Mucosal inflammation		
Investigations	Weight decreased	Amylase increased Lipase increased Blood thyroid stimulating hormone increased			

Adverse reactions from clinical studies are presented using frequencies for all-causality adverse events.
The following terms have been combined:

1. Goitre including goitre and toxic nodular goitre
2. Peripheral neuropathy including hyperaesthesia, hypoaesthesia, mononeuropathy, neuropathy peripheral, peripheral sensory neuropathy and paraesthesia
3. Dysgeusia including ageusia, dysgeusia and hypogeusia
4. Memory impairment including amnesia and memory impairment
5. PRES was not observed in patients treated with tivozanib in the five RCC monotherapy studies. One patient experienced Grade 4 PRES and hypertension in Study AV-951-09-901.
6. Vision impairment including reduced visual acuity, vision blurred and visual impairment
7. Myocardial infarction (acute) / ischaemia including acute myocardial infarction, ischaemia and myocardial infarction
8. Tachycardia including sinus tachycardia, supraventricular tachycardia, tachycardia and tachycardia paroxysmal
9. Haemorrhage including adrenal haemorrhage, anal haemorrhage, cervix haemorrhage uterine, duodenal ulcer haemorrhage, gingival bleeding, haematemesis, haemoptysis, haemorrhagic anaemia, haemorrhagic erosive gastritis, haemorrhagic stroke, mouth haemorrhage, pulmonary haemorrhage and respiratory tract haemorrhage
10. Arterial thromboembolism including acute myocardial infarction, arterial thrombosis, iliac artery thrombosis, ischaemic stroke, myocardial infarction and transient ischaemic attack
11. Venous thromboembolism including deep vein thrombosis, embolism venous and pulmonary embolism
12. Persistent severe hypertension including hypertensive crisis
13. Flushing including flushing and hot flush
14. Dyspnoea including dyspnoea and exertional dyspnoea
15. Abdominal pain including abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and abdominal rigidity
16. Stomatitis including oral discomfort, oral disorder and stomatitis
17. Pancreatitis including pancreatitis and pancreatitis acute
18. Dysphagia including dysphagia, odynophagia and oropharyngeal pain
19. Glossitis including glossitis and glossodynia
20. Gingivitis including gingival bleeding, gingival disorder, gingival pain and gingivitis
21. Alanine aminotransferase (ALT) increased / Aspartate aminotransferase (AST) increased including ALT increased and AST increased
22. Erythema including erythema, generalised erythema and palmar erythema
23. Pruritus including generalised pruritus and pruritus
24. Rash including rash, rash erythematous, rash generalised, rash maculo-papular, rash papular and rash pruritic
25. Acne including acne and dermatitis acneiform
26. Dermatitis including dermatitis and dermatitis bullous
27. Pain including bone pain, cancer pain, flank pain, groin pain, oral pain, pain, pain in extremity and tumour pain
28. Chest pain including chest pain and non-cardiac chest pain
29. Chills including chills and hypothermia

Description of selected adverse reactions

Hypertension

Hypertension was reported as an adverse reaction in 47.6% of patients receiving tivozanib as initial therapy; in 23.0% the hypertension was CTC ≥Grade 3. Persistent severe hypertension ('hypertensive crisis') was an adverse reaction in 1.0%, CTC Grade 3 or higher in 0.9%. One patient died as a result of uncontrolled hypertension in the setting of a suspected overdose.

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES (also known as reversible posterior leukoencephalopathy syndrome (RPLS)) was confirmed in one non-RCC patient after approximately 8 weeks on tivozanib. PRES is a neurological disorder that may present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present (see section 4.4).

Venous thromboembolism

Pulmonary embolism was reported in patients (0.7%) receiving tivozanib as initial therapy in the five core RCC monotherapy studies, with the majority CTC Grade ≥ 3 (see section 4.4). Deep vein thrombosis was also reported in two patients (0.3%) and was CTC Grade ≥ 3 in one patient (0.1%) receiving initial tivozanib therapy.

Arterial thromboembolic events

Arterial thromboembolic adverse reactions in the patients receiving tivozanib as initial therapy were ischaemic stroke (1.0%), myocardial infarction (0.7%), transient ischaemic attack (0.7%) and acute myocardial infarction (0.4%), the majority of which were at least CTC Grade 3, plus iliac artery thrombosis (0.1%). There were no deaths due to arterial thromboembolic adverse reactions in those receiving tivozanib as initial therapy but a myocardial infarction in a patient receiving second line tivozanib had a fatal outcome.

Cardiac failure

Pulmonary oedema was reported in two patients (0.3%) receiving tivozanib as initial therapy in the five core RCC monotherapy studies. Both events were CTC Grade 3 (see section 4.4).

QT/QTc prolongation

QT prolongation was reported in two patients (CTC Grade 2 and Grade 3) in the tivozanib cardiac safety study, neither reaction was considered serious (see section 4.4 and section 5.1).

Hypothyroidism

Hypothyroidism was reported as an adverse reaction for 5.6% of patients during initial therapy and was CTC Grade 2 or lower in all cases. It was reported as serious in one patient.

Haemorrhage

Haemorrhage adverse reactions were reported in the core monotherapy studies during initial treatment (see section 4.4).

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Two patients received excessive doses of tivozanib during the monotherapy studies. A patient with a history of hypertension experienced aggravated uncontrolled hypertension that was fatal after taking 3 doses of 1340 microgram tivozanib in one day (total 4020 microgram). No adverse reaction was experienced by the second patient who took 2 doses of 1340 microgram tivozanib in one day (total 2680 microgram).

Blood pressure should be well controlled prior to initiating tivozanib and patients should be monitored for hypertension during treatment (see section 4.4).

In cases of suspected overdose, tivozanib should be discontinued and the patient monitored for hypertension and treated as needed with standard anti-hypertensive therapy.

There is no specific treatment or antidote for tivozanib overdose.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors
ATC code: L01XE34

MECHANISM OF ACTION

Tivozanib potently and selectively blocks all 3 Vascular Endothelial Growth Factor receptors (VEGFR) and has been shown to block various VEGF induced biochemical and biologic responses *in vitro*, including VEGF ligand induced phosphorylation of all three VEGFR 1, 2 and 3, and proliferation of human endothelial cells. The next most potently inhibited kinase is c kit which is 8-fold less sensitive to inhibition by tivozanib compared to VEGFR 1, 2 and 3. VEGF is a potent mitogenic factor that plays a central role in angiogenesis and vascular permeability of tumour tissues. By blocking VEGF induced VEGFR activation, tivozanib inhibits angiogenesis and vascular permeability in tumour tissues, leading to inhibition of tumour growth *in vivo*.

CLINICAL EFFICACY AND SAFETY

The efficacy of tivozanib in the treatment of advanced RCC was studied in the following randomised clinical study.

Study AV-951-09-301

This controlled clinical study was a Phase 3 multi centre, open label, international, randomised study comparing tivozanib with sorafenib in patients with advanced RCC. Five hundred and seventeen (517) patients with recurrent or metastatic RCC with a clear cell component were randomised (1:1) to receive either tivozanib 1340 microgram once daily on a schedule of 3 weeks on treatment followed by 1 week off (schedule 3/1) or sorafenib 400 mg twice a day. The study included patients who had all undergone prior nephrectomy, and who had received either no prior therapy or no more than one prior systemic therapy in the metastatic setting (immunotherapy/chemotherapy); prior treatment with VEGF or mechanistic Target of Rapamycin (mTOR) targeted therapy was not allowed. Cross over to the tivozanib arm was permitted upon Response Evaluation Criteria In Solid Tumours (RECIST) defined progression on sorafenib according to the protocol of a separate extension study.

The primary endpoint of the study was progression free survival (PFS) by blinded independent radiology review; key secondary endpoints included overall survival (OS) and objective response rate (ORR) by independent radiology review.

The intent to treat (ITT) population included 517 patients, 260 randomised to tivozanib and 257 randomised to sorafenib. The baseline demographic and disease characteristics were generally well balanced across the tivozanib and sorafenib arms with regard to age (mean age 58.2 vs 58.4 years respectively), gender (71.2% vs 73.5% male respectively), race (95.8% vs 96.9% white respectively), geographic region (88.1% vs 88.7% from Central/Eastern Europe respectively) and prior treatment for metastatic RCC (69.6% vs 70.8% treatment naïve respectively). For the 30% of patients receiving prior treatment, the predominant therapy was interferon alpha as monotherapy which was received by 75 patients in the tivozanib arm and 62 patients in the sorafenib arm.

Tivozanib showed a statistically significant improvement in PFS and ORR over sorafenib by independent radiology review (Table 2 and Figure 1).

Figure 1: Kaplan Meier plot of progression free survival, independent radiological review (ITT Population).

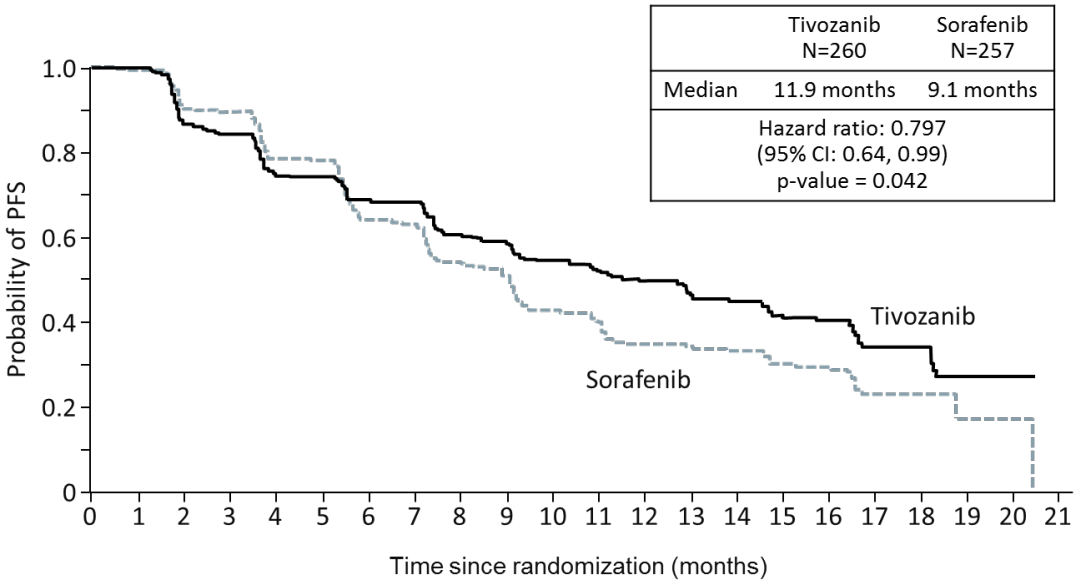

Table 2: Efficacy analysis by independent radiology review (ITT population)

	Tivozanib		Sorafenib		Hazard Ratio (95% CI)	P-value (Log rank test)
Progression-Free Survival [median, months (95% CI)], ITT Population	N=260	11.9 (9.3, 14.7)	N=257	9.1 (7.3, 9.5)	0.797 (0.639, 0.993)[a]	0.042[b]
Objective Response Rate (95% CI), ITT Population	N=260	33.1% (27.4, 39.2)	N=257	23.3% (18.3, 29.0)		0.014[c]
Progression-Free Survival, No prior treatment for Metastatic RCC Subgroup [median, months (95% CI)]	N=181	12.7 (9.1, 15.0)	N=181	9.1 (7.3, 10.8)	0.756 (0.580, 0.985)[d]	0.037[e]
Progression-Free Survival, One Prior Therapy for Metastatic Disease Subgroup [median, months (95% CI)]	N=78	11.9 (8.0, 16.6)	N=76	9.1 (7.2, 11.1)	0.877 (0.587, 1.309)[d]	0.520[e]

[a] Hazard ratio for tivozanib arm vs. sorafenib arm, based on stratified Cox proportional hazards model. Stratification factors are number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or ≥2). Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favour of tivozanib;

[b] p-value based on stratified log-rank test. Stratification factors are number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or ≥2);
[c] p-value based on stratified Cochran-Mantel-Haenszel (CMH) statistic. Stratification factors are number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or ≥2);
[d] Hazard ratio for tivozanib arm vs. sorafenib arm subgroup analyses, based on unstratified Cox proportional hazards model. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favour of tivozanib;
[e] p-value for subgroup analyses based on unstratified log-rank test.

OS was a key secondary endpoint in the pivotal study and the analysis included data from all randomized patients, including those who progressed on sorafenib and crossed over to receive tivozanib as part of the extension study. In the ITT population there was a small numerical difference between the two arms in terms of overall survival. median OS was 28.2 months (95% CI 22.5, 33.0) in the tivozanib arm compared to 30.8 months (95% CI 28.4, 33.3) in the sorafenib arm (HR=1.147, p=0.276).

Elderly patients
In a controlled clinical study (AV 951 09 301), in which 25% of patients receiving tivozanib were ≥ 65 years of age, no overall differences was observed in efficacy between elderly and younger patients (see section 4.2). In the core RCC studies some adverse reaction occurred more commonly in the elderly (see section 4.4).

Pharmacodynamic effects
In a cardiac safety study of 50 patients with advanced solid tumours treated with tivozanib at 1340 microgram daily for 21 days, the mean change from baseline in QTcF was 6.8 ms on day 21 of dosing. The maximum change in QTcF from baseline was 9.3 ms (90% CI: 5, 13.6), which occurred 2.5 hours after dosing on Day 21. The central tendency change for all measured days and across all time points was 2.2 ms. No subjects had a new > 500 ms change in QTcF; 2 patients (4%) had QTcF values > 480 ms. One subject (2%) had a > 60 ms change from baseline in QTcF and 6 subjects (12%) had a 30 ms to 60 ms change from baseline (see section 4.4 and section 4.8).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with tivozanib in all subsets of the paediatric population in advanced renal cell carcinoma (see section 4.2 for information on paediatric use).

5.2 PHARMACOKINETIC PROPERTIES

ABSORPTION
Following oral administration of tivozanib, peak serum levels are achieved after approximately 2 to 24 hours. After a single 1340 microgram dose, mean C_{max} was 10.2 to 25.2 ng/mL across healthy subject and patient studies. Single dose $AUC_{0\text{-}inf}$ for healthy volunteers dosed with 1340 microgram tivozanib was 1,950 to 2,491 ng.hr/mL. After once daily dosing of 1340 microgram tivozanib for 21 or 28 days in RCC patients, C_{max} was 67.5 to 94.3 ng/mL and $AUC_{0\text{-}24}$ was 1,180 to 1,641 ng.hr/mL. Exposure is dose proportional between 890 and 1340 microgram and dose related over the wider range of 450 mg and 1790 microgram. Accumulation at steady-state is approximately 6- to 7-fold the exposure observed at single-dose levels. Clearance is similar between acute and chronic dosing indicating no time dependent changes in PK.

When tivozanib was evaluated in a food effect study in healthy subjects, a high fat meal decreased the peak serum concentrations (C_{max}) by 23.4% compared to the fasted state. There was no effect of food on the overall exposure (AUC). Based on these data, tivozanib can be dosed with or without food (see section 4.2).

DISTRIBUTION
In vitro protein binding studies have shown that tivozanib is > 99% bound to plasma proteins. No concentration dependence of plasma protein binding was observed over the range of 0.1 to 5 µmol/L tivozanib. Albumin is the major tivozanib binding component in human plasma. *In vitro* studies have shown that tivozanib is neither a substrate nor an inhibitor of the multidrug efflux pump, P glycoprotein. *In vitro* studies suggest that tivozanib is an inhibitor of intestinal BCRP.

BIOTRANSFORMATION
In vitro metabolism studies have shown that CYP3A4 and CYP1A1 are capable of metabolising tivozanib. Unchanged tivozanib is the major circulating form of the molecule, and there were no major metabolites detected in serum at exposure equal to or greater than 10% of the total radioactivity exposure. As CYP1A1 is primarily expressed in extrahepatic tissues such as the lung and intestine, it was considered unlikely that this isoform would be extensively involved in hepatic metabolism.

In vitro studies have shown that metabolites of tivozanib can undergo UGT mediated biotransformation via the UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, and UGT1A10 pathways. Direct N-glucoronidation of tivozanib was a minor pathway of metabolism *in vitro*.

ELIMINATION
After chronic dosing of tivozanib in RCC patients for 21 days followed by 7 days without administration of tivozanib, tivozanib C_{min} is approximately 16.0 to 30.9 ng/mL.

In studies that evaluated the terminal elimination phase, tivozanib had a mean $t_{½}$ of 4.5 - 5.1 days. After a single dose oral dose of [^{14}C] tivozanib, approximately 79% of the radioactivity was recovered in the faeces and approximately 12% was found in the urine as metabolites. There was no unchanged tivozanib recovered in the urine indicating that tivozanib does not undergo renal excretion. [^{14}C] Tivozanib was the predominant drug-related material in faeces. There were no [^{14}C]-containing metabolites present in faeces at greater than 10% of the dose.

Special populations
Age, gender and race
Based on the population pharmacokinetic analysis, there is no clinically relevant effect of age, gender or race on the pharmacokinetics of tivozanib.

Hepatic impairment
Results from a single dose study to evaluate the pharmacokinetics, safety and tolerability of tivozanib in subjects with hepatic impairment show that across the entire measurement period, tivozanib was eliminated more slowly in subjects with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. Tivozanib exposure was increased in patients with severe hepatic impairment (mean $AUC_{0-\infty}$ by 4.0-fold) and in patients with moderate hepatic impairment (mean $AUC_{0-\infty}$ by 2.6-fold). No significant increase in exposure was observed in patients with mild (Child-Pugh Class A) hepatic impairment (mean $AUC_{0-\infty}$ by 1.2-fold). Tivozanib should be used with caution in patients with moderate hepatic impairment and the dose reduced to one 1340 microgram capsule every other day. Tivozanib should not be used in patients with severe hepatic impairment (see section 4.2 and section 4.4).

Renal impairment
Clinical studies with tivozanib were conducted in RCC patients with serum creatinine concentration ≤ 2 times the upper limit of normal, including those who may have had a prior nephrectomy. Although the impact of further impairment of renal function on the overall disposition of tivozanib is unknown, a clinical study has shown that no unchanged tivozanib is excreted in the urine indicating that tivozanib does not undergo renal excretion. According to the population pharmacokinetic analysis of tivozanib exposure, no dose adjustment is required in patients with mild or moderate renal impairment. Experience of tivozanib use in patients with severe renal impairment is limited and caution is advised.

CYP and UGT in vitro studies
In vitro studies with tivozanib indicate that it is not a CYP enzyme inducer. *In vitro* studies conducted in human liver microsomes and hepatocytes evaluating the activity of CYP1A2, CYP2B6, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 suggested that tivozanib is a weak inhibitor of CYP2B6 and CYP2C8. Based on the *in vitro* IC_{50} and *in vivo* unbound C_{max}, tivozanib was unlikely to interact in a clinically relevant manner with active substances that are metabolised by these enzyme pathways.

Studies conducted *in vitro* have shown that tivozanib is not a potent inhibitor of UGT (UDP-glucuronosyltransferase) metabolic activities and clinically relevant drug-drug interactions are unlikely with medicinal products metabolised by these pathways.

Transporter in vitro studies
In vitro studies have shown that tivozanib is neither a substrate nor inhibitor of the transporter proteins MDR1 (P-gp), OCT1, OATP1B1, OATP1B3 and BSEP. Furthermore, tivozanib was not an *in vitro* inhibitor of OAT1, OAT3, OCT2, MATE1 and MATE2-K or substrate of MRP2 and BCRP.

Tivozanib inhibits the transporter protein BCRP *in vitro*, at concentrations that are likely to restrict the effect to intestinal BCRP activity *in vivo*.

5.3 PRECLINICAL SAFETY DATA

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.

In repeat-dose toxicity studies in rats, abnormalities were noted in growing incisors (thin brittle teeth, tooth loss, malocclusions) at doses approximately 2-fold greater than the calculated human equivalent dose and growth plate hypertrophy was observed at doses approximately 0.7- to 7-fold greater than the calculated human equivalent dose. Tivozanib was shown to cause growth plate hypertrophy, absence of active corpora lutea and no maturing follicles in cynomolgus monkeys at dose levels that produced exposures equivalent to those seen at the recommended clinical dose.

Reproduction, mutagenesis, impairment of fertility
Tivozanib may impair human fertility. In nonclinical studies assessing mating and fertility parameters in male rats, doses > 2-fold higher than the recommended clinical dose, produced increased epididymis and testis weights associated with infertility. Increased testis weights were observed at a dose 7-fold higher than the recommended clinical dose. In female rats, an increase in non-viable foetuses was noted at a dose 0.7-fold the recommended clinical dose, while dose levels ≥ 2-fold the recommended clinical dose produced infertility.

Tivozanib was shown to be teratogenic, embryotoxic and foetotoxic in pregnant rats at dose levels 5 times lower than the recommended clinical dose (based on a 60 kg human). Studies in pregnant rabbits showed no effect on maternal health or embryo foetal development at doses approximately 0.6 times the human exposure at the recommended dose.

CARCINOGENICITY
Carcinogenicity studies have not been performed with tivozanib.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Fotivda 890 microgram hard capsules

Capsule content
Mannitol
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Indigo carmine (E132)
Yellow iron oxide (E172)

Printing ink (yellow)
Shellac
Propylene glycol
Strong ammonia solution
Titanium dioxide (E171)
Tartrazine aluminium lake (E102)

Printing ink (blue)
Shellac
Propylene glycol
Strong ammonia solution
Indigo carmine aluminium lake (E132)

Fotivda 1340 microgram hard capsules
Capsule content
Mannitol
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink (blue)
Shellac
Propylene glycol
Strong ammonia solution
Indigo carmine aluminium lake (E132)

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
5 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Keep the bottle tightly closed in order to protect from moisture.

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER
White HDPE bottle with a child resistant closure containing 21 hard capsules.
Each pack contains 1 bottle.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE
Prescription Only Medicine

8. SPONSOR

Link Pharmaceuticals Ltd.
Suite 32
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Medical Information
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9. DATE OF FIRST APPROVAL

25 July 2019

10. DATE OF REVISION OF THE TEXT

31 July 2020

Summary table of changes

Version of Data Sheet	Date of Medsafe Approval	Section Changed	Summary of New Information
2.0	21 January 2020	4.4 & 4.8	Addition of safety information relating to "Aneurysms and artery dissections" following update to Global Company Core Data Sheet
3.0	xx July 2020	8	Update to sponsor details due to product transfer.