ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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 Posology and method of administration

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

Posology

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 alanine 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 administration

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 medicinal product 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.

Posterior reversible encephalopathy syndrome (PRES)
In clinical studies, one case of 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 (HFSR)
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 (GI) perforation/fistula
It is recommended that symptoms of GI 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.

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.

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.

4.5 Interaction with other medicinal products 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			

System Organ Class	Very common	Common	Uncommon	Rare	Not known
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			
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		

System Organ Class	Very common	Common	Uncommon	Rare	Not known
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 of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein-kinase inhibitors, ATC code: L01EK03

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)

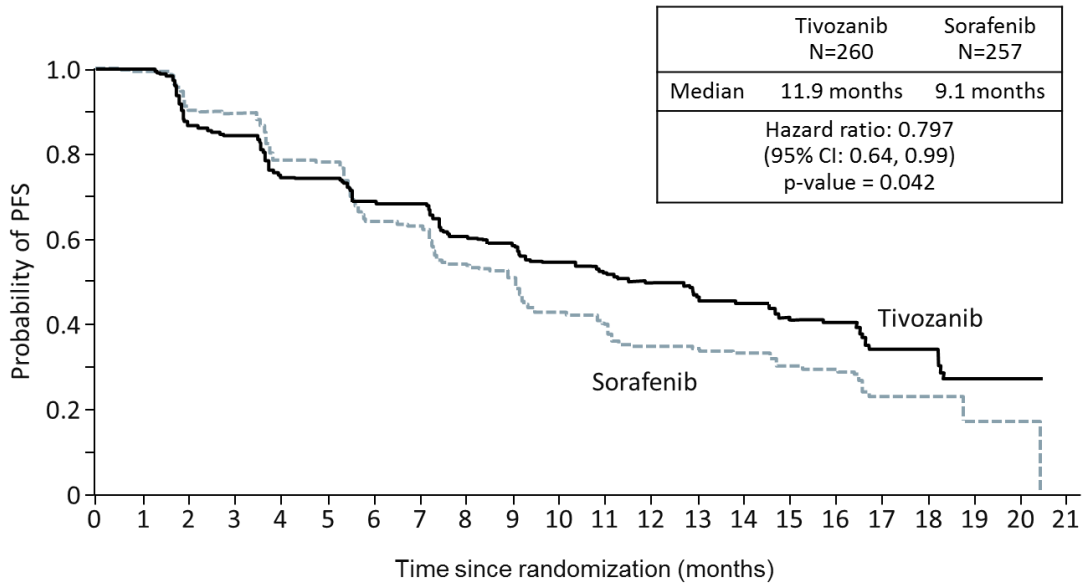


Table 2: Efficacy analysis by independent radiology review (ITT population)

	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 $\leq$ 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.

Carcinogenesis
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.

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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Recordati Netherlands B.V.
Beechavenue 54,
1119PW Schiphol-Rijk
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Fotivda 890 microgram hard capsules
EU/1/17/1215/001

Fotivda 1340 microgram hard capsules
EU/1/17/1215/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24/08/2017
Date of latest renewal: 15/07/2022

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

ALMAC PHARMA SERVICES (IRELAND) LIMITED
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Fotivda 890 microgram hard capsules
tivozanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains tartrazine. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Netherlands B.V.
Beechavenue 54,
1119PW Schiphol-Rijk
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1215/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fotivda 890 microgram

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Fotivda 890 microgram hard capsules
tivozanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains tartrazine. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Netherlands B.V.
Beechavenue 54,
1119PW Schiphol-Rijk
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Fotivda 1340 microgram hard capsules
tivozanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Netherlands B.V.
Beechavenue 54,
1119PW Schiphol-Rijk
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1215/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fotivda 1340 microgram

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Fotivda 1340 microgram hard capsules
tivozanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Netherlands B.V.
Beechavenue 54,
1119PW Schiphol-Rijk
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Fotivda 890 microgram hard capsules
Fotivda 1340 microgram hard capsules
tivozanib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Fotivda is and what it is used for

The active substance in Fotivda is tivozanib, which is a protein kinase inhibitor. Tivozanib reduces the supply of blood to the cancer, which slows down the growth and spread of cancer cells. It works by blocking the action of a protein called vascular endothelial growth factor (VEGF). Blocking the action of VEGF prevents the formation of new blood vessels.

Fotivda is used to treat adults with advanced kidney cancer. It is used where other treatments such as interferon-alpha or interleukin-2 have either not yet been used or have not helped to stop your disease.

2. What you need to know before you take Fotivda

Do not take Fotivda:
- If you are allergic to tivozanib or any of the other ingredients of this medicine (listed in section 6);
- If you are taking St. John's Wort (also known as *Hypericum perforatum*, a herbal remedy used for treatment of depression and anxiety).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Fotivda:
- if you have **high blood pressure**
  Fotivda can increase your blood pressure. Your doctor will monitor your blood pressure regularly and, if it is too high, may either give you a medicine to lower it, or reduce your dose of Fotivda. However, if your blood pressure remains too high, your doctor may decide to interrupt or to stop treatment with Fotivda. If you are already taking a medicine to treat high blood pressure, and your doctor reduces the dose of Fotivda or interrupts or stops treatment, you will be regularly checked for low blood pressure.

- if you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

- if you have had problems with **blood clots**
  Treatment with Fotivda may raise the risk of developing a blood clot (thrombus) in your blood vessels that could break loose and be carried by the blood stream to block another blood vessel. Tell your doctor if you have ever had one of the following:
  - a blood clot in your lungs (with cough, chest pain, sudden shortness of breath or coughing up blood)
  - blood clot in your legs or arms, eye, or brain (with pain or swelling in your hands or feet, reduced vision, or changes in your mental state)
  - a stroke, or signs and symptoms of a 'mini-stroke' (transient ischaemic attack)
  - a heart attack
  - high blood pressure
  - diabetes
  - major surgery
  - multiple injuries such as broken bones and damage to internal organs
  - inability to move for a long period
  - heart failure which can cause shortness of breath or ankle swelling
  - inability to breathe, bluish colour on your skin, fingertips or lips, restlessness, anxiety, confusion, altered consciousness or sense of awareness, rapid, shallow breathing, a racing heart or excessive sweating.

- if you suffer or have suffered from any of these symptoms or are treated for heart failure:
  - Shortness of breath (dyspnoea) when you exert yourself or when you lie down
  - Feeling weak and tired
  - Swelling (oedema) in your legs, ankles and feet
  - Reduced ability to exercise
  - Persistent cough or wheezing with white or pink blood-tinged phlegm

  Signs and symptoms of heart failure will be monitored whilst you are taking your medicine. If necessary, your doctor may reduce your dose of Fotivda, or interrupt or stop this treatment.

- If you have or are treated for an **abnormal rate and rhythm of the heartbeat (arrhythmia)**
  Your doctor will monitor the effect of Fotivda on your heart by recording the electrical activity of your heart (an electrocardiogram) or by measuring your blood calcium, magnesium and potassium levels during your treatment.

- if you have **problems with your liver**
  Your doctor will regularly monitor how well your liver is working before and during treatment with Fotivda (e.g. with blood tests), and if necessary may need to reduce how often you take Fotivda.

- if you have **problems with your thyroid gland** or **use medicines to treat thyroid disease**
  Treatment with Fotivda may cause your thyroid gland to work less well than usual. Your doctor will regularly monitor how well your thyroid gland is working before and during treatment with Fotivda (e.g. with blood tests).

Talk to your doctor, pharmacist or nurse while taking Fotivda:
- if you get **shortness of breath or ankle swelling**
  Tell your doctor right away as these may be symptoms of heart failure. Your doctor will monitor this, and depending on the severity may reduce your dose of Fotivda, or interrupt or stop treatment with Fotivda.

- if you have had problems with **bleeding**
  Treatment with Fotivda may increase the risk of bleeding. If you get bleeding problems (with painful swollen stomach (abdomen), vomiting blood, coughing up blood, black stools, blood in your urine, headache or changes in your mental state), tell your doctor right away. Treatment with Fotivda may need to be temporarily stopped.

- if laboratory tests show that there is **protein in your urine**
  Your doctor will monitor this at the beginning and during your treatment. Depending on the results, your doctor may reduce your dose of Fotivda, or interrupt or stop this treatment.

- if you suffer from a disease of the brain, called **posterior reversible encephalopathy syndrome (PRES)**
  Tell your doctor right away if you have symptoms such as headache, seizure (fit), lack of energy, confusion, blindness or other visual and neurologic disturbances such as weakness in an arm or a leg. If PRES is diagnosed, your doctor will stop treatment with Fotivda.

- if the **skin on the palms of your hands and the soles of your feet** become dry, cracked, scaling, or peeling, or is stinging or tingling
  These may be symptoms of a condition called hand foot skin reaction. Your doctor will treat the condition and, depending on the severity, the doctor may reduce your dose of Fotivda, or interrupt or stop this treatment.

- if you have symptoms of **gastrointestinal perforation or fistula** formation (developing a hole in the stomach or intestine or abnormal passages forming between parts of the intestine) such as severe stomach pain, chills, fever, nausea, vomiting or painful bowel obstruction, diarrhoea or rectal bleeding.
  Your doctor will regularly monitor you for these symptoms during your treatment with Fotivda.

- if you need to have an **operation or another form of surgery**
  Your doctor may recommend that you temporarily stop taking Fotivda if you have an operation or surgery, as it could affect wound healing.

Children and adolescents
Do not give Fotivda to children and adolescents under 18 years of age. This medicine has not been studied in children and adolescents.

Other medicines and Fotivda
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and other medicines you have bought without a prescription.

Fotivda may work less well when taken with some medicines. Tell your doctor if you are taking any of the following medicines; they may decide to change your medication:
- dexamethasone (a corticosteroid to reduce inflammation and treat disorders of the immune system);
- rosuvastatin (a medicine used to help lower cholesterol levels in your blood);
- phenobarbital, phenytoin, carbamazepine (used to treat epilepsy);
- nafcillin, rifampicin, rifabutin, rifapentin (antibiotics);
- St. John's Wort (also known as *Hypericum perforatum*, a herbal remedy used for treatment of depression and anxiety) as this herbal remedy should not be used at the same time as Fotivda.

Pregnancy, breast-feeding and fertility
- **Do not take Fotivda if you are pregnant.** Tell your doctor who will discuss with you the risks of taking Fotivda to you and your child.

- Both you and your partner must **use effective contraception.** If you or your partner are taking hormonal contraceptives (the pill, an implant or patch) you **must use an additional barrier method** throughout treatment and for another month after completing treatment.

- **Do not breast-feed during treatment with Fotivda**, as it is not known whether the active ingredient in Fotivda passes into breast-milk. Talk to your doctor if you are already breast-feeding.

- Talk to your doctor when planning a baby, as Fotivda may affect the **fertility** of men and women.

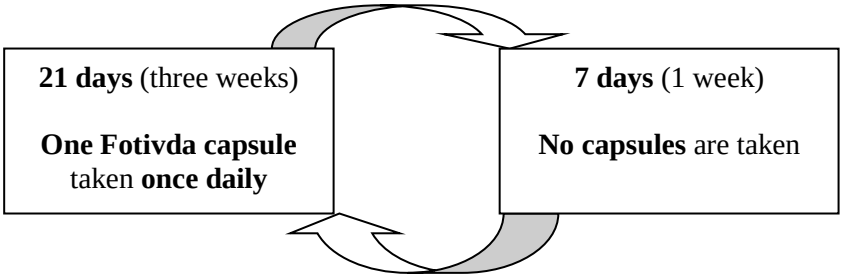
Driving and using machines
Fotivda can have side effects that may affect your ability to drive or use machines. Avoid driving or using machines if you feel weak, tired, or dizzy. See also Section 4 "Possible side effects".

Fotivda contains tartrazine (E102)
The printing ink used on the Fotivda 890 microgram capsule contains tartrazine (E102), which may cause allergic reactions.

3. How to take Fotivda

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Recommended dose
The recommended dose is one Fotivda 1340 microgram capsule, taken once daily for 21 days (3 weeks), followed by a 7-day (1-week) period when no capsules are taken.
This schedule is repeated in cycles of 4 weeks.



Your doctor will check you regularly, and you will normally continue to take Fotivda as long as it is working, and you do not suffer unacceptable side effects.

Reduced dose
In case you experience severe side effects, your doctor may decide to interrupt Fotivda therapy and/or lower the dose to:
One Fotivda 890 microgram capsule, taken once daily for 21 days (3 weeks), followed by a 7-day (1-week) period when no capsules are taken.
This schedule is repeated in cycles of 4 weeks.

Liver problems
If you have **liver problems**, your doctor may reduce how often you take your dose to every other day (i.e. one 1340 microgram capsule every other day).

Taking with food and drink
Fotivda must be taken with a glass of water and can be taken either with or without food. Swallow the capsule whole. Do not chew, dissolve or open the capsule before swallowing.

If you take more Fotivda than you should
Tell your doctor straightaway if you have taken more than your prescribed dose of 1 capsule per day.

Taking too much Fotivda makes side effects more likely or to become more severe, especially high blood pressure. Get **medical help straightaway** if you experience confusion, changes in your mental state or headaches. These are all symptoms of high blood pressure.

If you forget to take Fotivda
If you have missed taking a capsule, do **not** take a replacement capsule. Continue to take your next dose at the usual time.

Do not take a double dose to make up for a forgotten capsule.

If you vomit after taking Fotivda, do **not** take a replacement capsule. Continue to take your next dose at the usual time.

If you stop taking Fotivda
Do not stop taking this medicine unless your doctor tells you to. If you stop taking the capsules your condition may get worse.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

High blood pressure is the most serious and a very common side effect (see also in section 2 *"Warnings and Precautions"*).
Tell your doctor immediately if you think you have **high blood pressure.** Symptoms include severe headaches, blurred vision, shortness of breath, changes in your mental state, such as feeling anxious, confused or disorientated

Your doctor will check your blood pressure regularly during treatment with Fotivda. If you develop high blood pressure, your doctor may prescribe a medicine to treat your high blood pressure, lower your dose of Fotivda, or stop your treatment with Fotivda.

Other side effects

Very common (may affect more than 1 in 10 people)
- Difficulty speaking
- Diarrhoea
- Loss of appetite; weight loss
- Headache
- Difficult breathing; shortness of breath during exercise; coughing
- Tiredness; unusual weakness; pain (including in the mouth, bone, extremities, side of the body, groin, tumour)
- Inflammation of the mouth; slight mouth pain or discomfort; feeling sick; pain, discomfort and tightness in the stomach
- Hand-foot-syndrome with skin reddening, swelling, numbness and skin peeling on palms and soles
- Back pain
- Tiredness and lack of energy

Common (may affect up to 1 in 10 people)
- Underactive thyroid gland which may cause symptoms such as tiredness, lethargy, muscle weakness, slow heart rate, weight gain

- Unable to sleep
- Nerve damage including numbness, pins and needles, sensitive skin or numbness and weakness in the arms and legs
- Sight problems including blurred vision
- Rapid heart rate; tightness of the chest; heart attack/reduced blood flow to heart; blood clot in an artery (blood vessel)
- Blood clot in the lung. Symptoms include cough, chest pain, sudden shortness of breath or coughing up blood
- Blood clot in a deep vein such as in the leg
- Very high blood pressure leading to a stroke; flushed skin
- Nose bleed; runny nose; blocked nose
- Flatulence; heartburn; difficult and painful swallowing; sore throat; bloated stomach; swollen and painful tongue; inflamed painful and/or bleeding gums
- Taste changes or loss of taste
- Dizziness; ringing in the ears; dizziness and a spinning sensation (vertigo)
- Bleeding, e.g. in the brain, from the mouth, gums, lungs, stomach, gut ulcers, female genitals, anus, adrenal gland
- Coughing up blood; vomiting up blood
- Paleness and tiredness from excess bleeding
- Being sick; indigestion; constipation; dry mouth
- Itchy skin; rash; itching of the body; skin peeling; dry skin; hair loss; redness of the skin including the hands and body; acne
- Fever; chest pain; swelling of feet and legs; chills and low body temperature
- Joint pain; muscle pain
- Increased amount of protein in the urine
- Abnormal blood test results for liver, pancreas, kidney, and thyroid
- Inflammation of the pancreas causing severe stomach pain which may spread to your back

Uncommon (may affect up to 1 in 100 people)
- Rashes with pus; fungal infections
- Bruising easily, bleeding into the skin
- overactive thyroid gland (which may cause symptoms like increased appetite, loss of weight, intolerance to heat, increased sweating, tremors, rapid heart rate); enlarged thyroid gland.
- Increase in number of red blood cells
- Memory loss
- Temporary reduced blood flow to the brain
- Watery eyes
- Blocked ears
- Lack of blood flow through the heart blood vessels
- Peptic ulcer in the small intestines
- Red, swollen and sore skin; blistering skin; excessive sweating; hives
- Muscle weakness
- Swelling or irritation of the mucous membranes
- Abnormal electrocardiogram (ECG), rapid and/or irregular heart beat
- Heart failure. Symptoms include shortness of breath or ankle swelling. Swelling in the lungs caused by fluid build-up

Rare (may affect up to 1 in 1,000 people)
- Posterior reversible encephalopathy syndrome (PRES). Symptoms include headache, seizure, lack of energy, confusion, blindness or other visual and neurologic disturbances

Not known (cannot be estimated from available data).
- An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fotivda

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.

Keep the bottle tightly closed in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Fotivda contains

Fotivda 890 microgram hard capsules
The active substance is tivozanib. Each capsule contains tivozanib hydrochloride monohydrate equivalent to 890 microgram of tivozanib.
The other ingredients are:
- *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) (See Section 2 “Fotivda contains tartrazine (E102)”)
- *Printing ink, blue*: shellac, propylene glycol, strong ammonia solution, indigo carmine aluminium lake (E132).

Fotivda 1340 microgram hard capsules
The active substance is tivozanib. Each capsule contains tivozanib hydrochloride monohydrate equivalent to 1340 microgram of tivozanib.
The other ingredients are:
- *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).

What Fotivda looks like and contents of the pack
Fotivda 890 microgram hard capsules have a dark blue opaque cap and bright yellow opaque body, with “TIVZ” printed with yellow ink on the cap and “LD” on the body with dark blue ink.

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

Fotivda 890 microgram and Fotivda 1340 microgram are available as packs of 21 capsules in HDPE-bottles with child-resistant closure.

Marketing Authorisation Holder
Recordati Netherlands B.V.
Beechavenue 54,
1119PW Schiphol-Rijk
Netherlands

Manufacturer
ALMAC PHARMA SERVICES (IRELAND) LIMITED
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

This leaflet was last revised in {**MM/YYYY**}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.