1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS:

S4

1 NAME OF THE MEDICINE

Fotivda 890 microgram, hard capsule

Fotivda 1340 microgram, hard capsule

2 QUALITIVE AND QUANTITIVE COMPOSITION

Fotivda 890 microgram

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

Fotivda 1340 microgram

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

Contains sugar:

Fotivda 890 microgram and Fotivda 1340 microgram hard capsules contain sugar (mannitol 78,2 mg and 77,7 mg respectively).

For full list of excipients, see section 6.1.

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3 PHARMACEUTICAL FORM

Fotivda 890 microgram: Size 4 intact capsule containing white to off-white powder and consisting of:

Cap: Dark blue, opaque imprinted in yellow with “TIVZ”

Body: Bright yellow, opaque imprinted in dark blue with “LD”

Fotivda 1340 microgram: Size 4 intact capsule containing white to off-white powder and consisting of: Cap: Bright yellow, opaque imprinted in dark blue with “TIVZ”

Body: Bright yellow, opaque imprinted in dark blue with “SD”

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

Posology

Fotivda therapy should be supervised by a medical practitioner experienced in the use of anticancer therapies.

The recommended dose of Fotivda 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.

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Dose modification

The occurrence of undesirable effects may require temporary interruption and/or dose reduction of Fotivda 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 Fotivda 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 Fotivda in children and adolescents aged below 18 years have not been established. No data are available. There is no relevant use of Fotivda 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 Section 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

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experience and in patients undergoing dialysis as there is no experience of Fotivda 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 Fotivda.

Fotivda should not be used in patients with severe hepatic impairment. Patients with moderate hepatic impairment should only be treated with one Fotivda 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 5.1). No dose adjustment is required when administering Fotivda to patients with mild hepatic impairment. Fotivda 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 ingredient, tivozanib or to any of the excipients.

Co-administration with herbal preparations containing St. John's wort (*Hypericum perforatum*) (see Interactions).

Pregnancy and lactation.

Severe hepatic impairment (Child Pugh C).

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Uncontrolled severe hypertension.

Uncontrolled cardiac failure.

Uncontrolled hypothyroidism.

A history of recent venous thrombotic and/or arterial thrombotic events when other appropriate treatment options are available.

A history of previous posterior reversible encephalopathy syndrome (PRES).

An unresolved / not well controlled bleeding tendency.

4.4 Special warnings and precautions for use

There is evidence that the Progression Free Survival (PFS) of patients with non-clear cell renal cell carcinoma is less than in patients with clear cell renal cell carcinoma.

There is evidence that a nephrectomy prior to treatment with Fotivda improved PFS.

Hypertension

In clinical studies with Fotivda, 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 Fotivda. 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 Fotivda 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). Treatment should be discontinued in cases of persistent severe hypertension, posterior reversible encephalopathy syndrome (see below), or other complications of hypertension. Patients receiving anti-hypertensive medicine should still be monitored for hypotension when Fotivda is either interrupted or discontinued (see Section 4.3).

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Arterial thromboembolic events

In clinical studies with Fotivda, 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. Fotivda has not been studied in patients who had an ATE within the preceding 6 months of clinical study initiation. Fotivda 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) (see Section 4.3).

Venous thromboembolic events

In clinical studies with Fotivda, 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. Fotivda has not been studied in patients who had a VTE within the preceding 6 months of clinical study initiation (see Section 4.3).

Cardiac failure

In clinical studies with Fotivda, as monotherapy for the treatment of patients with RCC, cardiac failure has been reported (see Section 4.8 ~~SIDE EFFECTS~~). Signs or symptoms of cardiac failure should be frequently monitored throughout treatment with Fotivda. 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 (see Section 4.3).

Haemorrhage

In clinical studies with Fotivda, haemorrhagic events have been reported (see Section 4.8).

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Fotivda 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, Fotivda should be temporarily interrupted (see Section 4.3).

Proteinuria

Proteinuria has been reported in clinical studies with Fotivda (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 Fotivda has to be reduced or the treatment temporarily interrupted. If the patient develops Grade 4 proteinuria (nephrotic syndrome) Fotivda has to be discontinued. Risk factors for proteinuria include high blood pressure.

Hepatotoxicity

In clinical studies with Fotivda, 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 Fotivda because of the potential risk of hepatotoxicity (see Section 4.2).

Fotivda should not be used in patients with severe hepatic impairment (see Section 4.3). Patients with moderate hepatic impairment should only be treated with one Fotivda 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 Fotivda to patients with mild hepatic impairment. Fotivda should be used with caution in patients with mild and moderate hepatic impairment with close monitoring of tolerability.

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Posterior reversible encephalopathy syndrome

In clinical studies, one case of posterior reversible encephalopathy syndrome (PRES) was confirmed after treatment with Fotivda (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. Fotivda must be discontinued in patients developing signs or symptoms of PRES. The safety of re-initiating Fotivda therapy in patients previously experiencing PRES is not known and Fotivda should only be used with caution in these patients (see Section 4.3).

Hand foot skin reaction

In clinical studies with Fotivda, 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 Fotivda) (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 Fotivda, QT/QTc interval prolongation has been reported (see Section 4.8 and 5.2). QT/QTc interval prolongation may lead to an increased risk for ventricular dysrhythmias. It is recommended that Fotivda be used with caution in patients with a history of QT interval prolongation or other relevant pre-existing cardiac disease and those receiving other medicines known to increase the QT interval. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium)

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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 Fotivda and that Fotivda should be used with caution in patients at risk for GI perforation or fistula.

Wound healing complications

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

Hypothyroidism

In clinical studies with Fotivda, hypothyroidism has been reported (see Section 4.8). Hypothyroidism has been observed to occur at any time during treatment with Fotivda, developing as early as within two months of treatment initiation. Risk factors for hypothyroidism include prior history of hypothyroidism and use of anti-thyroid medicines. Thyroid function should be monitored before initiation of, and periodically throughout treatment with Fotivda. Hypothyroidism should be treated according to standard medical practice (see Section 4.3).

Adrenal glands

Adrenal cortical damage has been reported in preclinical studies in rats and monkeys at exposures to tivozanib not much higher than expected therapeutic tivozanib exposure in humans.

Although the relevance of this finding in humans is unknown, adrenal cortical function should

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be monitored if needed and patients should be observed for signs and symptoms of adrenal cortical insufficiency and treated if necessary.

Elderly patients

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

Contains sugar:

Fotivda 890 microgram and Fotivda 1340 microgram hard capsules contain sugar (mannitol 78,2 mg and 77,7 mg respectively), which may have an effect on diabetes mellitus.

Tartrazine:

The printing ink used on the Fotivda 890 microgram capsule contains tartrazine (E102), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of Tartrazine sensitivity in the general population is currently thought to be low, it is frequently seen in patients who also have aspirin sensitivity.

4.5 Interaction with other medicines and other forms of interaction

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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 Fotivda 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 Fotivda 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 Fotivda 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, contained in Fotivda, 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.

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Medicines for which intestinal absorption is restricted by BCRP

Fotivda 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 Fotivda 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 Fotivda 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 Fotivda. Female partners of male patients taking Fotivda 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 Fotivda may reduce the effectiveness of hormonal contraceptives and therefore women using hormonal contraceptives should add a barrier method.

Pregnancy

Fotivda should not be used during pregnancy or if pregnancy is planned.

Studies in animals have shown reproductive toxicity and teratogenicity in rats (see Section 4.3)

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Breastfeeding

Because of the potential for tivozanib-mediated adverse reactions in breastfed infants, women should not breastfeed their babies while taking Fotivda (see Section 4.3).

Fertility

Animal studies indicate that male and female fertility may be affected by treatment with Fotivda.

Conservation of sperms or ova should be considered before treatment with Fotivda.

4.7 Effects on ability to drive and use machines

Fotivda may have an 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

a. Summary of the safety profile

Pooled data of 674 patients with advanced RCC who continued to receive Fotivda 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 Fotivda.

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 Fotivda 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

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adverse reactions leading to Fotivda dose reduction/ interruption were hypertension (4,7 %), diarrhoea (3,1 %), fatigue (1,8 %).

In patients receiving Fotivda 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 list of adverse reactions

Adverse reactions occurring in patients who continued to receive Fotivda 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.

System Organ Class	**Very common**	**Common**	**Uncommon**	**Rare**	**Frequency 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			

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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 Electro-cardiogram QT prolonged		
Vascular disorders	Hypertension	Haemorrhage[9] Arterial thromboembolism[10] Venous thromboembolism[11] Persistent severe hypertension[12] Flushing[13]	Vascular disorders		Aneurysms and artery dissections

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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			

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Skin and subcutaneous tissue disorders	Palmar-plantar erythro-dysaesthesia 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			

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		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

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[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

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Description of selected adverse reactions

Hypertension

Hypertension was reported as an adverse reaction in 47,6 % of patients receiving Fotivda 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 Fotivda. 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 Fotivda 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 Fotivda therapy.

Arterial thromboembolic events

Arterial thromboembolic adverse reactions in the patients receiving Fotivda 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

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adverse reactions in those receiving Fotivda as initial therapy but a myocardial infarction in a patient receiving second-line Fotivda had a fatal outcome.

Cardiac failure

Pulmonary oedema was reported in two patients (0,3 %) receiving Fotivda 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 Fotivda cardiac safety study, neither reaction was considered serious (see Section 4.4 and 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 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 to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

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4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity.

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

In cases of suspected overdose, Fotivda 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 Fotivda overdose. Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.26 Cytostatic medicines

Pharmacotherapeutic group and ATC code:

Antineoplastic agents, protein-kinase inhibitors, ATC code: L01EK03

Pharmacodynamic effects:

Tivozanib is an antineoplastic medicine and protein-kinase inhibitor.

Tivozanib 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. 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*.

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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 1950 to 2491 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 1180 to 1641 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.

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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-glucuronidation 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:

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

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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.

Hepatic impairment

Results from a single dose study to evaluate the pharmacokinetics, safety and tolerability of tivozanib in subjects with hepatic impairment show that 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 4.3, 4.2 and 4.4).

Elderly patients, 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.

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,

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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 medicines 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fotivda 890 microgram

Excipients:

Capsule content:

Mannitol, magnesium stearate.

Capsule shell:

Gelatine, titanium dioxide (E171), indigo carmine (E132), yellow iron oxide. (E172).

Printing ink (yellow):

Shellac, propylene glycol, strong ammonia solution, titanium dioxide (E171), tartrazine

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aluminium lake (E102).

Printing ink (blue):

Shellac, propylene glycol, strong ammonia solution, indigo carmine aluminium lake (E132).

Excipients with known effect:

Each hard capsule contains trace amounts of tartrazine (E102) (8 – 12 % of the yellow printing ink composition)

Fotivda 1340 microgram

Excipients:

Capsule content:

Mannitol, magnesium stearate.

Capsule shell:

Gelatine, titanium dioxide (E171), yellow iron oxide (E172)

Printing ink (blue)

Shellac, propylene glycol, strong ammonia solution, indigo carmine aluminium lake (E132)

Contains sugar:

Fotivda 890 microgram and Fotivda 1340 microgram hard capsules contain sugar (mannitol 78,2 mg and 77,7 mg respectively).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

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6.4 Special precautions for storage

Store at or below 25 °C.

Keep the bottle tightly closed to protect from moisture.

Store in the original container.

6.5 Nature and contents of container

White HDPE bottle with a white child resistant polypropylene closure containing 21 hard capsules. Each bottle is packed into an outer cardboard carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 The holder of the certificate of registration

Key Oncologics (Pty) ltd.

39 Eleventh Avenue

Hougton Estate, 2198

South Africa

8 Registration number(s)

FOTIVDA 890 µg: 53/26/0503

FOTIVDA 1340 µg: 53/26/0504

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9 Date of first authorisation/renewal of the authorisation

Date of registration: 1 September 2020

10 Date of revision of text

7 February 2022

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