INLYTA™

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product name

INLYTA™

1.2 Strength

1 and 5 mg

1.3 Pharmaceutical dosage form

Film-coated tablet

2. QUALITITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative declaration

Axitinib

2.2 Quantitative declaration

Each film-coated tablet contains axitinib 1 mg or 5 mg.

3. PHARMACEUTICAL FORM

The 1 mg tablets are red oval film-coated and debossed ‘Pfizer’ on one side and ‘1XNB’ on the other.

The 5 mg tablets are red triangular film-coated and debossed ‘Pfizer’ on one side and ‘5XNB’ on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Axitinib is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy (see also Section 5.1).

4.2 Posology and method of administration

The recommended starting oral dose of axitinib is 5 mg twice daily. Axitinib may be taken with or without food.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

Dose adjustments

Dose increase or reduction is recommended based on individual safety and tolerability.

Patients who tolerate the axitinib starting dose of 5 mg twice daily with no adverse reactions >Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]) for two consecutive weeks, are normotensive, and are not receiving antihypertensive medication, may have their dose increased to 7 mg twice daily. Subsequently, using the same criteria, patients who tolerate the axitinib dose of 7 mg twice daily, may have their dose increased to a maximum of 10 mg twice daily.

Management of some adverse drug reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy. When dose reduction is necessary, the axitinib dose may be reduced to 3 mg twice daily and further to 2 mg twice daily.

Dose adjustment is not required on the basis of patient age, race, gender, or body weight.

Concomitant strong CYP3A4/5 inhibitors

Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib to approximately half the dose (e.g., from a starting dose of 5 mg twice daily to a reduced dose of 2 mg twice daily) is recommended. If co-administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered.

Concomitant strong CYP3A4/5 inducers

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, and *Hypericum perforatum* [also known as St. John's wort]) may decrease axitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 induction potential is recommended. Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inducers, if a strong CYP3A4/5 inducer must be co-administered, a gradual dose increase of axitinib is recommended. If the dose of axitinib is increased, the patient should be monitored carefully for toxicity. If co-administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer.

Use in pediatrics

The safety and efficacy of axitinib in children (<18 years) have not been established. No data are available.

Use in the elderly

No dose adjustment is required (see Section 5.2).

Hepatic impairment:

No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) [e.g., the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily]. Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Renal impairment:

No dose adjustment is required (see Section 5.2).

4.3 Contraindications

None

4.4 Special warnings and precautions for use

Cardiac failure events

In a controlled clinical study with axitinib for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiopulmonary failure, left ventricular dysfunction, and right ventricular failure) were reported in 6/359 patients (1.7%) receiving axitinib and 3/355 patients (0.8%) receiving sorafenib. Grade 3/4 cardiac failure events were observed in 2/359 patients (0.6%) receiving axitinib and 1/355 patients (0.3%) receiving sorafenib. Fatal cardiac failure was reported in 2/359 patients (0.6%) receiving axitinib and 1/355 patients (0.3%) receiving sorafenib.

In clinical studies with axitinib for the treatment of patients with RCC, cardiac failure events (including cardiac failure, congestive cardiac failure, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 12/672 patients (1.8%) receiving axitinib. Grade 3/4 cardiac failure events were reported in 7/672 patients (1.0%) and fatal cardiac failure events were reported in 2/672 patients (0.3%) receiving axitinib.

Monitor for signs or symptoms of cardiac failure periodically throughout treatment with axitinib. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of axitinib therapy.

Hypertension

In a controlled clinical study with axitinib for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving axitinib and 103/355 patients (29%) receiving sorafenib. Grade 3 hypertension was observed in 55/359 patients (15%) receiving axitinib and 38/355 patients (11%) receiving sorafenib and Grade 4 hypertension was observed in 1/359 patients (<1%) receiving axitinib and 1/355 patients (<1%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) receiving axitinib and none of the patients (0%) receiving sorafenib. The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of axitinib or sorafenib treatment and blood pressure increases have been observed as early as 4 days after starting axitinib. Hypertension was managed with standard antihypertensive therapy. Discontinuation of axitinib treatment due to hypertension occurred in 1/359 patients (<1%) receiving axitinib and none of the patients (0%) receiving sorafenib.

In pooled clinical studies with axitinib for the treatment of patients with RCC, hypertension was reported in 344/672 patients (51%) receiving axitinib. Grade 3 hypertension was reported in 148/672 patients (22%) receiving axitinib. Grade 4 hypertension was reported in 7/672 patients (1%) receiving axitinib.

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In the case of persistent hypertension despite use of antihypertensive medications, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib treatment and restart at a lower dose once the patient is normotensive (see Section 4.2). If axitinib is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

Aneurysms and artery dissections

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

Thyroid dysfunction

In a controlled clinical study with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 69/359 patients (19%) receiving axitinib and 29/355 patients (8%) receiving sorafenib. Hyperthyroidism was reported in 4/359 patients (1%) receiving axitinib and 4/355 patients (1%) receiving sorafenib. In patients who had thyroid stimulating hormone (TSH) <5 μU/mL before treatment, elevations of TSH to ≥10 μU/mL occurred in 79/245 patients (32%) receiving axitinib and 25/232 patients (11%) receiving sorafenib.

In pooled clinical studies with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 165/672 patients (25%) receiving axitinib. Hyperthyroidism was reported in 11/672 patients (2%) receiving axitinib.

Monitor thyroid function before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism and hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Arterial thromboembolic events

In a controlled clinical study with axitinib for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving axitinib and 4/355 patients (1%) receiving sorafenib. The most frequent arterial thromboembolic event was transient ischemic attack (1%). Fatal cerebrovascular accident was reported in 1/359 patients (<1%) receiving axitinib

and none of the patients receiving sorafenib.

In pooled clinical studies with axitinib for the treatment of patients with RCC, arterial thromboembolic events were reported in 19/672 patients (3%) receiving axitinib. Grade 3 arterial thromboembolic events were reported in 8/672 patients (1%). Grade 4 arterial thromboembolic events were reported in 9/672 patients (1%). Fatal arterial thromboembolic events were reported in 2 patients (<1%) receiving axitinib.

In monotherapy studies with axitinib, arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion) were reported in 16/699 patients (2%).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial thromboembolic event within the previous 12 months.

Venous thromboembolic events

In a controlled clinical study with axitinib for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving axitinib and 2/355 patients (1%) receiving sorafenib. Grade 3/4 venous thromboembolic events were reported in 9/359 patients (3%) receiving axitinib (including pulmonary embolism, deep vein thrombosis, and retinal-vein occlusion/thrombosis) and 2/355 patients (1%) receiving sorafenib. Fatal pulmonary embolism was reported in 1/359 patients (<1%) receiving axitinib and none of the patients (0%) receiving sorafenib.

In pooled clinical studies with axitinib for the treatment of patients with RCC, venous thromboembolic events were reported in 19/672 patients (3%) receiving axitinib. Grade 3 venous thromboembolic events were reported in 6/672 patients (1%). Grade 4 venous thromboembolic events were reported in 8/672 patients (1%). Fatal venous thromboembolic events were reported in 1/672 patients (<1%) receiving axitinib.

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had a venous thromboembolic event within the previous 6 months.

Elevation of hemoglobin or hematocrit

Increases in hemoglobin or hematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib. An increase in red blood cell mass may increase the risk of thromboembolic events.

Elevated hemoglobin above the upper limit of normal (ULN) was observed in 31/320 patients (10%) receiving axitinib and 3/316 patients (1%) receiving sorafenib.

Monitor hemoglobin or hematocrit before initiation of, and periodically throughout, treatment with axitinib. If hemoglobin or hematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease hemoglobin or hematocrit to an acceptable level.

Hemorrhage

In a controlled clinical study with axitinib for the treatment of patients with RCC, in which patients with untreated brain metastasis were excluded, hemorrhagic events were reported in 58/359 patients (16%) receiving axitinib and 64/355 patients (18%) receiving sorafenib. The most common hemorrhagic events in patients treated with axitinib were epistaxis (6%), hematuria (3%), hemoptysis (2%), and rectal hemorrhage (2%). Grade 3/4 hemorrhagic events were reported in 5/359 patients (1%) receiving axitinib (including cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal hemorrhage, and melaena) and 11/355 (3%) patients receiving sorafenib. Fatal hemorrhage was reported in 1/359 patients (<1%) receiving axitinib (gastric hemorrhage) and 3/355 patients (1%) receiving sorafenib.

In pooled clinical studies with axitinib for the treatment of patients with RCC, hemorrhagic events were reported in 173/672 patients (26%) receiving axitinib. Grade 3 hemorrhagic events were reported in 20/672 patients (3%). Grade 4 hemorrhagic events were reported in 7/672 patients (1%) and fatal hemorrhagic events were reported in 3/672 patients (<1%) receiving axitinib.

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Gastrointestinal perforation and fistula formation

In a controlled clinical study with axitinib for the treatment of patients with RCC, gastrointestinal

perforation was reported in 1/359 patients (<1%) receiving axitinib and none of the patients (0%) receiving sorafenib. In addition to cases of gastrointestinal perforation, fistulas were reported in 2/359 patients (1%) receiving axitinib and 1/355 patients (<1%) receiving sorafenib. In pooled clinical studies with axitinib for the treatment of patients with RCC, gastrointestinal perforation and fistula were reported in 13/672 patients (2%) receiving axitinib. In monotherapy studies with axitinib (N=699), fatal gastrointestinal perforation was reported in 1/699 patient (<1%).

Monitor for symptoms of gastrointestinal perforation periodically throughout treatment with axitinib.

Wound healing complications

No formal studies of the effect of axitinib on wound healing have been conducted.

Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Reversible posterior leukoencephalopathy syndrome

In a controlled clinical study with axitinib for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 1/359 patients (<1%) receiving axitinib and none of the patients (0%) receiving sorafenib.

In pooled clinical studies with axitinib for the treatment of patients with RCC, RPLS was reported in 2/672 patients (<1%) receiving axitinib.

RPLS 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 RPLS. In patients with signs/symptoms of RPLS, temporarily interrupt or permanently discontinue axitinib. The safety of reinitiating axitinib therapy in patients previously experiencing RPLS is not known.

Proteinuria

In a controlled clinical study with axitinib for the treatment of patients with RCC, proteinuria was reported in 39/359 patients (11%) receiving axitinib and 26/355 patients (7%) receiving sorafenib. Grade 3 proteinuria was reported in 11/359 patients (3%) receiving axitinib and 6/355 patients (2%) receiving sorafenib.

In pooled clinical studies with axitinib for the treatment of patients with RCC, proteinuria was reported in 142/672 patients (21%) receiving axitinib. Grade 3 proteinuria was reported in 32/672 patients (5%) receiving axitinib. Grade 4 proteinuria was reported in 1/672 patients (<1%) receiving axitinib.

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment.

Elevation of liver enzymes

In a clinical dose-finding study, concurrent elevations of alanine aminotransferase [ALT] (12 times the ULN) and bilirubin (2.3 times the ULN), considered to be drug-related hepatotoxicity, were observed in 1 patient who received axitinib at a starting dose of 20 mg twice daily (4 times the recommended starting dose). In a controlled clinical study with axitinib for the treatment of patients with RCC, no concurrent elevations of ALT (>3 times the ULN) and bilirubin (>2 times the ULN) were observed for axitinib (N=359) or sorafenib (N=355).

Monitor liver function tests before initiation of, and periodically throughout, treatment with axitinib.

Hepatic impairment

In clinical studies with axitinib, the systemic exposure to axitinib was approximately 2-fold higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that axitinib is metabolized primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 inhibitors

Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean area under the curve (AUC) 2-fold and C_{max} 1.5-fold of a single 5-mg oral dose of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5

inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose adjustment of axitinib is recommended (see Section 4.2).

CYP3A4/5 inducers

Rifampin, a strong inducer of CYP3A4/5, administered at a dose of 600 mg once daily for 9 days, reduced the mean AUC by 79% and C_{max} by 71% of a single 5-mg dose of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, and *Hypericum perforatum* [also known as St. John's wort]) may decrease axitinib plasma concentrations. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of axitinib is recommended (see Section 4.2).

***In vitro* studies of CYP and UGT inhibition and induction**

In vitro studies indicated that axitinib does not inhibit CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations.

In vitro studies indicated that axitinib has a potential to inhibit CYP1A2. Therefore, co-administration of axitinib with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g., theophylline).

In vitro studies also indicated that axitinib has the potential to inhibit CYP2C8. However, co-administration of axitinib with paclitaxel, a known CYP2C8 substrate, did not result in increased plasma concentrations of paclitaxel in patients with advanced cancer, indicating lack of clinical CYP2C8 inhibition.

In vitro studies in human hepatocytes also indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5. Therefore, co-administration of axitinib is not expected to reduce the plasma concentration of co-administered CYP1A1, CYP1A2, or CYP3A4/5 substrates *in vivo*.

***In vitro* studies with P-glycoprotein**

In vitro studies indicated that axitinib inhibits P-glycoprotein. However, axitinib is not expected to

inhibit P-glycoprotein at therapeutic plasma concentrations. Therefore, co-administration of axitinib is not expected to increase the plasma concentration of digoxin, or other P-glycoprotein substrates, *in vivo*.

4.6 Fertility, pregnancy and lactation

Fertility

Based on non-clinical findings, axitinib has the potential to impair reproductive function and fertility in humans (see Section 5.3).

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving axitinib.

Pregnancy

Axitinib may cause fetal harm when administered to a pregnant woman. Studies in pregnant mice have shown that axitinib caused toxic effects to the fetus (see Section 5.3).

There are no adequate and well-controlled studies in pregnant women using axitinib. Women of childbearing potential should be advised to avoid becoming pregnant while receiving axitinib. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

Lactation

No studies have been conducted in humans to assess the effect of axitinib on milk production, its presence in breast milk, or its effects on the breast-fed child. It is unknown whether axitinib is excreted in human milk.

Since many drugs are commonly excreted in human milk, and because of the potential for serious adverse reactions in nursing infants due to exposure to axitinib, a decision should be made whether to discontinue nursing or to discontinue axitinib, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

No studies on the effect of axitinib on the ability to drive and use machines have been performed. Patients should be advised that they may experience events, such as dizziness and/or fatigue

during treatment with axitinib.

4.8 Undesirable effects

The safety of axitinib has been evaluated in 672 patients with advanced RCC who participated in the pivotal randomized clinical study or 4 additional monotherapy studies with axitinib. The data described below reflect exposure to axitinib in 359 patients with advanced RCC who participated in a randomized clinical study versus sorafenib.

The median duration of treatment was 6.4 months (range 0.03 to 22.0) for patients who received axitinib and 5.0 months (range 0.03 to 20.1) for patients who received sorafenib. Dose modifications or temporary delay of treatment due to an adverse event occurred in 199/359 patients (55%) receiving axitinib and 220/355 patients (62%) receiving sorafenib. Permanent discontinuation due to an adverse event occurred in 33/359 patients (9%) receiving axitinib and 46/355 patients (13%) receiving sorafenib.

The most common (≥20%) adverse reactions observed following treatment with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthsia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation.

The following risks, including appropriate action to be taken, are discussed in greater detail in Section 4.4: cardiac failure events, hypertension, thyroid dysfunction, arterial thromboembolic events, venous thromboembolic events, elevation of hemoglobin or hematocrit, haemorrhage, gastrointestinal perforation and fistula formation, wound healing complications, RPLS, proteinuria, and elevation of liver enzymes.

Table 1 presents adverse reactions reported in patients who received axitinib or sorafenib.

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: 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), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1. Adverse Reactions Reported in the RCC Study in Patients Who Received Axitinib or Sorafenib

SYSTEM ORGAN CLASS	Frequency Category	Preferred Term[a]	Axitinib (N=359)		Sorafenib (N=355)	
			All Grades[b]	Grade ≥3	All Grades[b]	Grade ≥3
			%	%	%	%
Blood and lymphatic system disorders	Common	Anaemia	3.6	0.6	11.5	3.9
	Uncommon	Polycythaemia	0.8	0.3	0	0
Endocrine disorders	Very Common	Hypothyroidism	19.2	0.3	8.2	0
	Common	Hyperthyroidism	1.1	0	1.1	0.3
Metabolism and nutrition disorders	Very Common	Decreased appetite	34.0	5.0	28.5	3.7
	Common	Dehydration	6.4	3.6	2.5	1.1
		Hyperkalaemia	3.1	1.4	2.3	0.8
		Hypercalcaemia	2.8	0.3	1.7	0.6
Nervous system disorders	Very Common	Headache	13.6	0.6	11.3	0
		Dysgeusia	10.6	0	8.2	0
	Common	Dizziness	9.2	0.6	4.2	0
	Uncommon	Reversible Posterior Leukoencephalopathy Syndrome	0.3	0.3	0	0
Ear and labyrinth disorders	Common	Tinnitus	3.1	0	0.8	0
Cardiac disorders	Common	Cardiac failure events[c]	1.7	1.1	0.8	0.6
Vascular disorders	Very Common	Hypertension	40.4	15.6	29.0	11.0
		Haemorrhage[d]	16.2	1.7	18.0	3.9
	Common	Venous embolic and thrombotic events[e]	3.1	2.8	0.6	0.6
		Arterial embolic and thrombotic events[f]	1.4	1.4	1.1	1.1
	Uncommon	Hypertensive crisis	0.6	0.6	0	0

SYSTEM ORGAN CLASS	Frequency Category	Preferred Term[a]	Axitinib (N=359)		Sorafenib (N=355)	
			All Grades[b]	Grade ≥3	All Grades[b]	Grade ≥3
			%	%	%	%
Respiratory, thoracic and mediastinal disorders	Very Common	Dyspnoea	14.8	2.5	12.1	2.8
		Cough	15.3	0.8	16.6	0.6
		Dysphonia	30.9	0	13.5	0
Gastrointestinal disorders	Very Common	Diarrhoea	54.9	10.6	53.2	7.3
		Vomiting	23.7	3.3	17.2	0.8
		Nausea	32.3	2.5	21.7	1.1
		Abdominal pain	14.2	2.2	10.7	0.8
		Stomatitis	15.0	1.4	12.4	0.3
		Constipation	20.3	1.1	20.3	0.8
		Dyspepsia	10.0	0	2.3	0
	Common	Upper abdominal pain	8.1	0.8	3.9	0.3
		Haemorrhoids	4.2	0	1.4	0.3
		Glossodynia	3.1	0	1.1	0
	Uncommon	Gastrointestinal perforation and fistula[g]	0.8	0	0.3	0
Hepatobiliary disorders	Uncommon	Hyperbilirubinaemia	0.8	0.3	0.8	0.6
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia (hand-foot syndrome)	27.3	5.0	51.0	16.1
		Rash	12.5	0.3	31.5	3.9
		Dry skin	10.0	0	10.7	0
	Common	Erythema	2.2	0	10.1	0.3
		Pruritus	6.7	0	12.4	0
		Alopecia	3.9	0	32.4	0
Musculoskeletal	Very Common	Arthralgia	15.0	1.9	11.0	1.4

SYSTEM ORGAN CLASS	Frequency Category	Preferred Term[a]	Axitinib (N=359)		Sorafenib (N=355)	
			All Grades[b]	Grade ≥3	All Grades[b]	Grade ≥3
			%	%	%	%
and connective		Pain in extremity	12.5	0.6	13.5	0.6
tissue disorders	Common	Myalgia	7.0	0.8	2.8	0
Renal and	Very Common	Proteinuria	10.9	3.1	7.3	1.7
urinary disorders	Common	Haematuria	3.3	0.3	2.0	0
General	Very Common	Fatigue	39.0	11.4	31.5	5.1
disorders and		Asthaenia	20.6	5.3	14.1	2.5
administration		Mucosal inflammation	15.3	1.4	12.4	0.6
site conditions						
Investigations	Very Common	Weight decreased	24.8	2.2	20.8	1.4
	Common	Lipase increased	2.5	0.6	5.4	3.4
		Creatinine increased	2.8	0.3	0.8	0
		Alanine aminotransferase increased	2.2	0.3	3.7	1.7
		Alkaline phosphatase increased	1.9	0.3	2.0	0
		Aspartate aminotransferase increased	1.1	0.3	3.7	1.1
		Amylase increased	1.7	0	3.9	0.3

SYSTEM ORGAN CLASS	Frequency Category	Preferred Term[a]	Axitinib (N=359)		Sorafenib (N=355)	
			All Grades[b]	Grade ≥3	All Grades[b]	Grade ≥3
			%	%	%	%

[a] Adverse reactions are listed according to treatment-emergent, all-causality frequency.

[b] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

[c] Cardiac failure events includes the following preferred terms (All Grades frequency): cardiac failure (0.6%), cardiopulmonary failure (0.6%), left ventricular dysfunction (0.3%), and right ventricular failure (0.3%).

[d] Haemorrhage includes the following preferred terms (All Grades frequency): epistaxis (6.1%), haematuria (3.3%), haemoptysis (2.2%), rectal haemorrhage (2.2%), cerebral haemorrhage (0.3%), gastric haemorrhage (0.3%), and lower gastrointestinal haemorrhage (0.3%).

[e] Venous embolic and thrombotic events includes the following preferred terms (All Grades frequency): pulmonary embolism (1.9%), retinal vein occlusion/thrombosis (0.6%), and deep vein thrombosis (0.6%).

[f] Arterial embolic and thrombotic events includes the following preferred terms (All Grades frequency): transient ischaemic attack (0.8%) and cerebrovascular accident (0.3%). In monotherapy studies with axitinib, myocardial infarction was also reported (0.1%).

[g] Gastrointestinal perforation and fistula includes the following preferred terms (All Grades frequency): fistula (0.3%), anal fistula (0.3%), and gastrointestinal perforation (0.3%).

4.9 Overdose

There is no specific treatment for axitinib overdose.

In a controlled clinical study with axitinib for the treatment of patients with RCC, 1 patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with axitinib, patients who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal hemoptysis.

In cases of suspected overdose, axitinib should be withheld and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumor growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumor vasculature that expressed the target *in vivo* and produced tumor growth delay, regression, and inhibition of metastases in many experimental models of cancer.

Pharmacodynamics effects

In a randomized, 2-way crossover study, 35 healthy subjects were administered a single oral dose of axitinib (5 mg) in the absence and presence of 400 mg ketoconazole for 7 days. Results of this study indicated that axitinib plasma exposures up to 2-fold greater than the therapeutic levels expected following a 5 mg dose did not produce clinically-significant QT interval prolongation.

Clinical efficacy

The safety and efficacy of axitinib were evaluated in a randomized, open-label, multicenter Phase 3 study. Patients (N=723) with advanced RCC whose disease had progressed on or after treatment with 1 prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomized (1:1) to receive axitinib (n=361) or sorafenib (n=362). The primary endpoint, progression-free survival (PFS), was assessed using a blinded independent central review. Secondary endpoints included objective response rate (ORR) and overall survival (OS).

Of the patients enrolled in this study, 389 patients (54%) had received 1 prior sunitinib-based therapy, 251 patients (35%) had received 1 prior cytokine-based therapy (interleukin-2 or interferon-alfa), 59 patients (8%) had received 1 prior bevacizumab-based therapy, and 24 patients (3%) had received 1 prior temsirolimus-based therapy. The baseline demographic and disease characteristics were similar between the axitinib and sorafenib groups with regard to age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.

There was a statistically significant advantage for axitinib over sorafenib for the primary endpoint of PFS (see Table 2 and Figure 1). There was no statistically significant difference between the

arms in OS.

Table 2. Efficacy Results by Independent Assessment

Endpoint/Study Population	Axitinib	Sorafenib	HR (95% CI)	P-value
PFS[a,b]				
Overall ITT	N=361	N=362		
Median, months (95% CI)	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)	0.67 (0.54, 0.81)	<0.0001[c]
Sunitinib-refractory subgroup	N=194	N=195		
Median, months (95% CI)	4.8 (4.5, 6.4)	3.4 (2.8, 4.7)	0.74 (0.57, 0.96)	0.0107[d]
Cytokine-refractory subgroup	N=126	N=125		
Median, months (95% CI)	12.1 (10.1, 13.9)	6.5 (6.3, 8.3)	0.46 (0.32, 0.68)	<0.0001[d]
OS				
Median, months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	0.374[e]
ORR	N=361	N=362		
% (95% CI)	19.4 (15.4, 23.9)	9.4 (6.6, 12.9)	2.06[f] (1.41, 3.00)	0.0001[g]

CI: Confidence interval; HR: Hazard ratio (axitinib/sorafenib); ITT: Intent to treat; ORR: Objective response rate; PFS: Progression-free survival; OS: Overall survival.

[a] Time from randomization to progression or death due to any cause, whichever occurs first.

[b] Assessed by independent radiology review according to RECIST.

[c] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy (comparison is considered statistically significant if the one-sided p-value is <0.023).

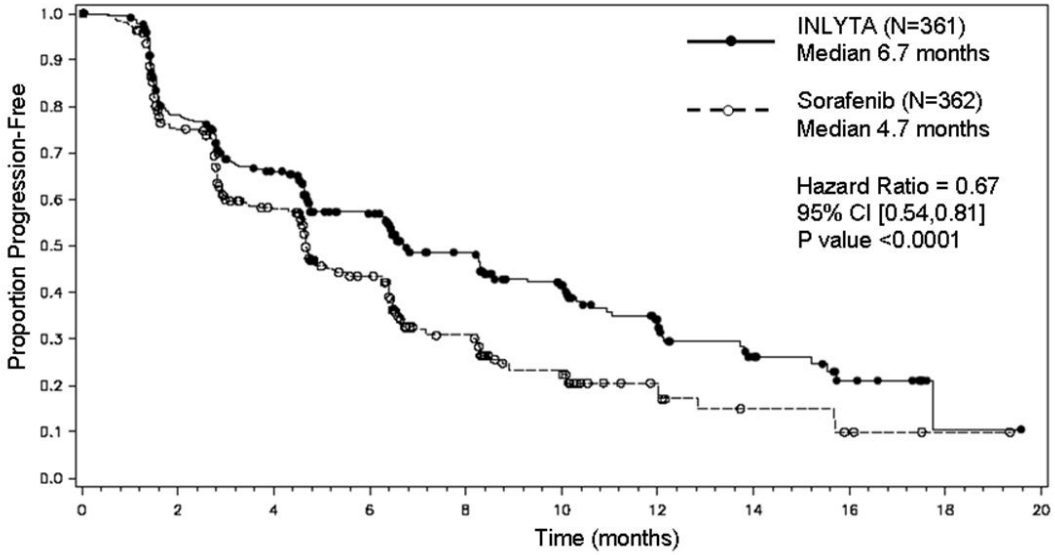
[d] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

[e] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy.

[f] Risk ratio is used for ORR. A risk ratio >1 indicated a higher likelihood of responding in the axitinib arm; a risk ratio <1 indicated a higher likelihood of responding in the sorafenib arm.

[g] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior therapy.

Figure 1. Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Overall Population



5.2 Pharmacokinetic properties

After oral administration of axitinib tablets, the mean absolute bioavailability is 58% compared to intravenous administration. The plasma half-life of axitinib ranges from 2.5 to 6.1 hours. Dosing of axitinib at 5 mg twice daily resulted in <2-fold accumulation compared to administration of a single dose. Based on the short half-life of axitinib, steady state is expected within 2 to 3 days of the initial dose.

Absorption and distribution

Peak axitinib concentrations in plasma are generally reached within 4 hours following oral administration of axitinib with the median T_{max} ranging from 2.5 to 4.1 hours. Administration of axitinib with a moderate fat meal resulted in 10% lower exposure compared to overnight fasting. A high fat, high-calorie meal resulted in 19% higher exposure compared to overnight fasting. Axitinib may be administered with or without food.

The average C_{max} and AUC increased proportionally over an axitinib dosing range of 5 to 10 mg. *In vitro* binding of axitinib to human plasma proteins is >99% with preferential binding to albumin and moderate binding to α_1-acid glycoprotein. At the 5 mg twice daily dose in the fed state, the geometric mean peak plasma concentration and 24-hour AUC were 27.8 ng/mL and 265 ng.h/mL, respectively, in patients with advanced RCC. The geometric mean oral clearance and apparent volume of distribution were 38 L/h and 160 L, respectively.

Metabolism and elimination

Axitinib is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. Following oral administration of a 5-mg radioactive dose of axitinib, 30-60% of the radioactivity was recovered in feces and 23% of the radioactivity was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in feces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity.

The sulfoxide and N-glucuronide metabolites show approximately 400-fold and 8000-fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

Special populations

Gender, race, and age

Population pharmacokinetic analyses in patients with advanced cancer (including advanced RCC) and healthy volunteers indicate that there are no clinically relevant effects of age, gender, body weight, race, renal function, UGT1A1 genotype, or CYP2C19 genotype.

Pediatric population

Axitinib has not been studied in patients <18 years of age.

Hepatic impairment

In vitro and *in vivo* data indicate that axitinib is primarily metabolized by the liver. Compared to subjects with normal hepatic function, systemic exposure following a single dose of axitinib was similar in subjects with mild hepatic impairment (Child-Pugh class A) and higher (approximately 2-fold) in subjects with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

Renal impairment

Unchanged axitinib is not detected in the urine.

Axitinib has not been studied in subjects with renal impairment. In clinical studies with axitinib for

the treatment of patients with RCC, patients with serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min were excluded.

Population pharmacokinetic analyses have shown that axitinib clearance was not altered in subjects with renal impairment and no dose adjustment of axitinib is required.

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been performed with axitinib.

Genotoxicity

Axitinib was tested using a series of genetic toxicology assays consisting of *in vitro* bacterial reverse mutation (Ames), human lymphocyte chromosome aberration, and *in vivo* mouse bone marrow micronucleus assays. Axitinib was not mutagenic or clastogenic in these assays.

Impairment of fertility

Axitinib has the potential to impair reproductive function and fertility in humans. Findings in the male reproductive tract were observed in the testes/epididymis (decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms) at $\geq$100 mg/kg/day in mice (approximately 306 times the AUC at the recommended starting dose in humans) and $\geq$3 mg/kg/day in dogs (approximately 0.5 times the AUC at the recommended starting dose in humans). Findings in the female reproductive tract in mice and dogs included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at $\geq$10 mg/kg/day (approximately equivalent to the AUC at the recommended starting dose in humans).

Axitinib did not affect mating or fertility in male mice at any dose tested up to 100 mg/kg/day. However, reduced testicular weights, sperm density and count were noted at $\geq$30 mg/kg/day (approximately 72 times the AUC at the recommended starting dose in humans) following at least 70 days of treatment with axitinib. No adverse male reproductive effects in mice were noted at 10 mg/kg/day (approximately 21 times the AUC at the recommended starting dose in humans). In female mice, reduced fertility and embryonic viability were observed at all doses tested ($\geq$30 mg/kg/day) following at least 15 days of treatment with axitinib (approximately 64 times the AUC at the recommended starting dose in humans).

Developmental toxicity

Pregnant mice exposed to axitinib at an oral dose level of 3 mg/kg/day (approximately 3 times the AUC at the recommended starting dose in humans), showed an increased occurrence of cleft palate and common variations in skeletal ossification. No fetal alterations were observed in mice at a dose level of 1 mg/kg/day (approximately equivalent to the AUC at the recommended starting dose in humans).

Toxicity studies in juvenile animals

Physeal dysplasia was observed in immature mice and dogs given axitinib at doses of $\geq$30 mg/kg/day for at least 1 month (approximately 37 times the AUC at the recommended starting dose in humans); the incidence and severity were dose-related and the effects were reversible when treatment stopped. Dental caries were observed in mice treated for more than 1 month at axitinib doses of $\geq$10 mg/kg/day (approximately 9 times the AUC at the recommended starting dose in humans); residual findings, indicative of partial reversibility, were observed when treatment stopped. For physeal dysplasia, no effect levels of 10 mg/kg/day in mice (approximately 8 times the AUC at the recommended starting dose in humans) and 10 mg/kg/day in dogs (approximately equivalent to the AUC at the recommended starting dose in humans) were determined in animals given axitinib for 1 month. A no effect level was not defined for caries of the incisors in mice. Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient

Tablets contain microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate. Film-coat contains hydroxypropylmethylcellulose, titanium dioxide, lactose monohydrate, triacetin, red iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Please see details on carton.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Foil/foil blisters containing 1, 7 or 14 tablets. Packs containing 1, 2, 4 or 8 blister.

High-density polyethylene (HDPE) bottle with dessicant and a polypropylene closure containing 60 or 180 tablets.

7. MARKETING AUTHORIZATION HOLDER

Pfizer (Thailand) Limited

8. MARKETING AUTHORIZATION NUMBERS

1C 86/57 (N), 1C 87/57 (N)

9. DATE OF AUTHORIZATION

07 September 2017

10. DATE OF REVISION OF THE TEXT

11 January 2020

Warnings (based on the Ministry of Public Health Announcement)

This drug may cause serious harm, should be used under the supervision of a physician.