1. NAME OF THE MEDICINAL PRODUCT
INLYTA®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 1 mg or 5 mg axitinib.

3. PHARMACEUTICAL FORM
Film-coated tablet

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
INLYTA® is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

4.2 Posology and method of administration
Posology
The recommended starting oral dose of INLYTA® is 5 mg twice daily. Administer INLYTA® doses approximately 12 hours apart with or without food (see Section **5.2 Pharmacokinetic properties**). INLYTA® should be swallowed whole with a glass of water.

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.

Over the course of treatment, patients who tolerate INLYTA® for at least two consecutive weeks with no adverse reactions >Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]), are normotensive, and are not receiving anti-hypertensive medication, may have their dose increased. When a dose increase from 5 mg twice daily is recommended, the INLYTA® dose may be increased to 7 mg twice daily, and further to 10 mg twice daily using the same criteria.

Over the course of treatment, management of some adverse drug reactions may require temporary interruption or permanent discontinuation and/or dose reduction of INLYTA® therapy (see Section **4.4 Special warnings and precautions for use**). If dose reduction from 5 mg twice daily is required, the recommended dose is 3 mg twice daily. If additional dose reduction is required, the recommended dose is 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

The concomitant use of strong CYP3A4/5 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although INLYTA® 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 INLYTA® by approximately half is recommended, as this dose reduction is predicted to adjust the axitinib area under the plasma concentration versus time curve (AUC) to the range observed without inhibitors. The subsequent doses can be increased or decreased based on individual safety and tolerability. If co-administration of the strong inhibitor is discontinued, the INLYTA® dose should be returned (after 3 – 5 half-lives of the inhibitor) to that used prior to initiation of the strong CYP3A4/5 inhibitor (see Sections **4.5 Interaction with other medicinal products and other forms of interaction, *CYP3A4/5 inhibitors* and 5.2 Pharmacokinetic properties)**.

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 INLYTA® in pediatric patients have not been studied.

Use in the elderly
No dosage adjustment is required in elderly patients (see Section **5.2 Pharmacokinetic properties**).

Hepatic impairment
No starting dose adjustment is required when administering INLYTA® to patients with mild hepatic impairment (Child-Pugh class A). Based on the pharmacokinetic data, the INLYTA® starting dose should be reduced by approximately half in patients with baseline moderate hepatic impairment (Child-Pugh class B). The subsequent doses can be increased or decreased based on individual safety and tolerability. INLYTA® has not been studied in patients with severe hepatic impairment (Child-Pugh class C) (see Sections **4.4 Special warnings and precautions for use**, ***Elevation of liver enzymes*** and **5.2 Pharmacokinetic properties, *Special populations***).

Renal impairment
No starting dose adjustment is needed for patients with pre-existing mild to severe renal impairment (see Section **5.2 Pharmacokinetic properties, *Special populations***).

4.3 Contraindications
None

4.4 Special warnings and precautions for use

Cardiac failure events

In a controlled clinical study with INLYTA® 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 INLYTA® and 3/355 patients (0.8%) receiving sorafenib. Grade 3/4 cardiac failure events were observed in 2/359 patients (0.6%) receiving INLYTA® and 1/355 patients (0.3%) receiving sorafenib. Fatal cardiac failure was reported in 2/359 patients (0.6%) receiving INLYTA® and 1/355 patients (0.3%) receiving sorafenib.

In clinical studies with INLYTA® for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 12/672 patients (1.8%) receiving INLYTA®. 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 INLYTA®.

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

Hypertension

In a controlled clinical study with INLYTA® for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving INLYTA® and 103/355 patients (29%) receiving sorafenib. Grade 3 hypertension was observed in 55/359 patients (15%) receiving INLYTA® and 38/355 patients (11%) receiving sorafenib and Grade 4 hypertension was observed in 1/359 patients (<1%) receiving INLYTA® and 1/355 patients (<1%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) receiving INLYTA® 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 INLYTA® or sorafenib treatment and blood pressure increases have been observed as early as 4 days after starting INLYTA®. Hypertension was managed with standard anti-hypertensive therapy. Discontinuation of INLYTA® treatment due to hypertension occurred in 1/359 patients (<1%) receiving INLYTA® and none of the patients (0%) receiving sorafenib.

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

Blood pressure should be well-controlled prior to initiating INLYTA®. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensive medications, the INLYTA® dose should be reduced. For patients who develop severe hypertension, temporarily interrupt INLYTA® treatment and restart at a lower dose once the patient is normotensive (see Section **4.2 Posology and method of administration**). If INLYTA® is interrupted, patients receiving anti-hypertensive 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 INLYTA®, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

In pooled clinical studies with axitinib for the treatment of patients with RCC, aneurysms and artery dissections was not reported in patients receiving INLYTA®.

Thyroid dysfunction
In a controlled clinical study with INLYTA® for the treatment of patients with RCC, hypothyroidism was reported in 69/359 patients (19%) receiving INLYTA® and 29/355 patients (8%) receiving sorafenib. Hyperthyroidism was reported in 4/359 patients (1%) receiving INLYTA® 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 INLYTA® and 25/232 patients (11%) receiving sorafenib**.**

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

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

Arterial thromboembolic events
In a controlled clinical study with INLYTA® for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving INLYTA® 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 INLYTA® and none of the patients (0%) receiving sorafenib.

In pooled clinical studies with INLYTA® for the treatment of patients with RCC, arterial thromboembolic events were reported in 19/672 patients (3%) receiving INLYTA®. 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 INLYTA®.

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

INLYTA® should be used with caution in patients who are at risk for, or who have a history of, these events. INLYTA® 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 INLYTA® for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving INLYTA® and

2/355 patients (1%) receiving sorafenib. Grade 3/4 venous thromboembolic events were reported in 9/359 patients (3%) receiving INLYTA® (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 INLYTA® and none of the patients receiving sorafenib.

In pooled clinical studies with INLYTA® for the treatment of patients with RCC, venous thromboembolic events were reported in 19/672 patients (3%) receiving INLYTA®. 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 INLYTA®.

INLYTA® should be used with caution in patients who are at risk for, or who have a history of, these events. INLYTA® 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 INLYTA® 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 INLYTA® 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 INLYTA® (including cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal hemorrhage, and melena) and 11/355 patients (3%) receiving sorafenib. Fatal hemorrhage was reported in 1/359 patients (<1%) receiving INLYTA® (gastric hemorrhage) and 3/355 patients (1%) receiving sorafenib.

In pooled clinical studies with INLYTA® for the treatment of patients with RCC, hemorrhagic events were reported in 173/672 patients (26%) receiving INLYTA®. 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 INLYTA®.

INLYTA® 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 INLYTA® dose.

Gastrointestinal perforation and fistula formation
In a controlled clinical study with INLYTA® for the treatment of patients with RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving INLYTA® 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 INLYTA® for the treatment of patients with RCC, gastrointestinal perforation and fistula were reported in 13/672 patients (2%) receiving INLYTA®. 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 INLYTA®.

Wound healing complications
No formal studies of the effect of INLYTA® on wound healing have been conducted.

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

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

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

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 INLYTA®. The safety of reinitiating INLYTA® therapy in patients previously experiencing RPLS is not known.

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

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

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

Elevation of liver enzymes
In a controlled clinical study with INLYTA® for the treatment of patients with RCC, alanine aminotransferase (ALT) elevations of all grades occurred in 22% of patients on both arms, with Grade 3/4 events in <1% of patients on the INLYTA® arm and 2% of patients on the sorafenib arm.

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 INLYTA® at a starting dose of 20 mg twice daily (4 times the recommended starting dose). In a controlled clinical study with INLYTA® 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 INLYTA® (N = 359) or sorafenib (N = 355).

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

Hepatic impairment
In clinical studies with INLYTA®, the systemic exposure to INLYTA® 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 INLYTA® to patients with moderate hepatic impairment (Child-Pugh class B). INLYTA® has not been studied in patients with severe hepatic impairment (Child-Pugh class C) (see Section **4.2 Posology and method of administration**, ***Dose adjustments***).

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 INLYTA® with strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations and should be avoided. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided. 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 INLYTA® is recommended (see Section **4.2 Posology and method of administration**).

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 INLYTA® 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. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and

should be avoided if possible. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of INLYTA® is recommended (see Section **4.2 Posology and method of administration**).

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, INLYTA® is not expected to inhibit P-glycoprotein at therapeutic plasma concentrations. Therefore, co-administration of INLYTA® 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, INLYTA® has the potential to impair reproductive function and fertility in humans (see Section **5.3 Preclinical safety data**).

Women of child-bearing potential
Women of childbearing potential should be advised to avoid becoming pregnant while receiving INLYTA®.

Pregnancy
INLYTA® may cause fetal harm when administered to a pregnant woman based on its mechanism of action. Studies in pregnant mice have shown that axitinib caused toxic effects to the fetus (see Section **5.3 Preclinical safety data**).

There are no adequate and well-controlled studies in pregnant women using INLYTA®. Women of childbearing potential should be advised to avoid becoming pregnant while receiving INLYTA®. If this drug is used during pregnancy, or if the 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 not known 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 INLYTA®, a decision should be made whether to discontinue nursing or to discontinue INLYTA®, 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 INLYTA® 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 INLYTA®.

4.8 Undesirable effects

The safety of INLYTA® has been evaluated in 672 patients with advanced RCC who participated in the pivotal randomized clinical study or 4 additional monotherapy studies with INLYTA®. The data described below reflect exposure to INLYTA® 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 INLYTA® 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 reaction occurred in 199/359 patients (55%) receiving INLYTA® and 220/355 patients (62%) receiving sorafenib. Permanent discontinuation due to an adverse reaction occurred in 33/359 patients (9%) receiving INLYTA® and 46/355 patients (13%) receiving sorafenib.

The most common (≥20%) adverse reactions observed following treatment with INLYTA® were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (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 Special warnings and precautions for use**: cardiac failure events, hypertension, thyroid dysfunction, arterial thromboembolic events, venous thromboembolic events, elevation of hemoglobin or hematocrit, hemorrhage, 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 INLYTA® 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	Adverse Reaction[a]	Axitinib (N = 359)		Sorafenib (N = 355)	
			All Grades[b]	Grade ≥3	All Grades[b]	Grade ≥3
			%	%	%	%
Blood and lymphatic system disorders	Common	Anemia	3.6	0.6	11.5	3.9
	Uncommon	Polycythemia	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
		Hyperkalemia	3.1	1.4	2.3	0.8
		Hypercalcemia	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
		Hemorrhage[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
Respiratory, thoracic and mediastinal disorders	Very Common	Dyspnea	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	Diarrhea	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
		Hemorrhoids	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

System Organ Class	Frequency Category	Adverse Reaction[a]	Axitinib (N = 359)		Sorafenib (N = 355)	
			All Grades[b]	Grade ≥3	All Grades[b]	Grade ≥3
			%	%	%	%
Hepatobiliary disorders	Uncommon	Hyperbilirubinemia	0.8	0.3	0.8	0.6
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysesthesia (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 and connective tissue disorders	Very Common	Arthralgia	15.0	1.9	11.0	1.4
		Pain in extremity	12.5	0.6	13.5	0.6
	Common	Myalgia	7.0	0.8	2.8	0
Renal and urinary disorders	Very Common	Proteinuria	10.9	3.1	7.3	1.7
General disorders and administration site conditions	Very Common	Fatigue	39.0	11.4	31.5	5.1
		Asthenia	20.6	5.3	14.1	2.5
		Mucosal inflammation	15.3	1.4	12.4	0.6
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

[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] Hemorrhage includes the following preferred terms (All Grades frequency): epistaxis (6.1%), hematuria (3.3%), hemoptysis (2.2%), rectal hemorrhage (2.2%), cerebral hemorrhage (0.3%), gastric hemorrhage (0.3%), and lower gastrointestinal hemorrhage (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 ischemic 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 INLYTA® overdose.

In a controlled clinical study with INLYTA® 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 INLYTA®, 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, INLYTA® 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 receptors (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 INLYTA® (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 INLYTA® 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 INLYTA® (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 INLYTA® 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 INLYTA® 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	INLYTA®	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 (INLYTA®/sorafenib); ITT: Intent to treat; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free 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).

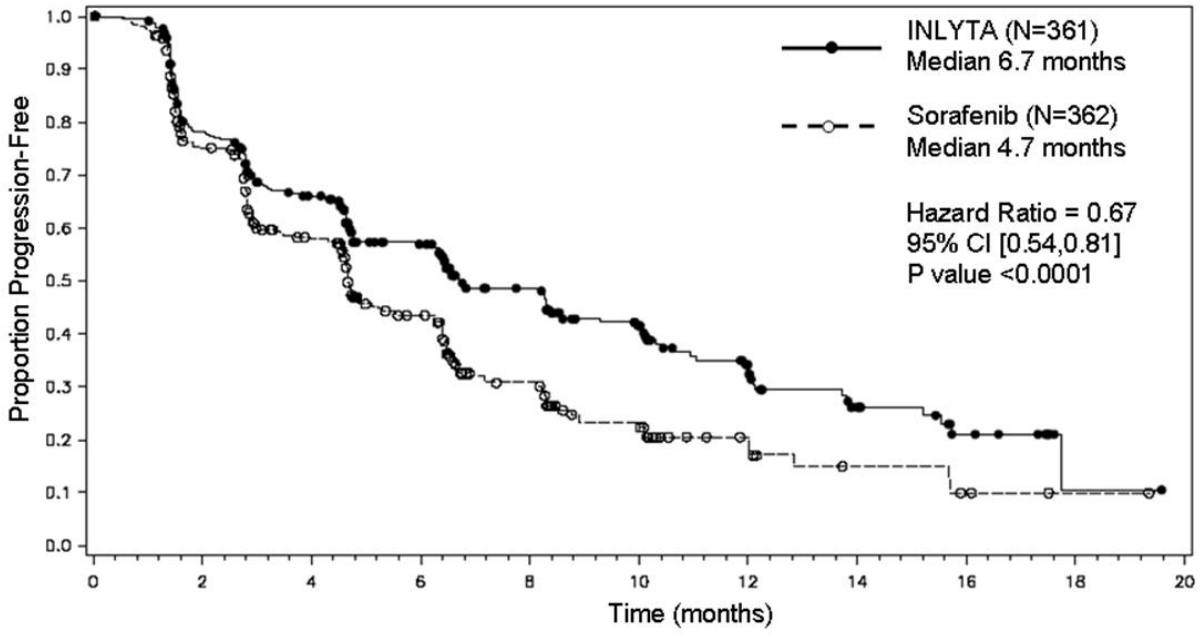
[d] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

[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 INLYTA® 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 INLYTA® 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. INLYTA® 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 8,000-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
INLYTA® 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 INLYTA® 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

INLYTA® 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 ≥100 mg/kg/day in mice (approximately 306 times the AUC at the recommended starting dose in humans) and ≥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 ≥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 ≥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 10m g/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 (≥30/mg/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 ≥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 ≥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 excipients

INLYTA® is supplied as red, film-coated tablets containing either 1 mg or 5 mg of axitinib together with microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry® II red 32K15441 as inactive ingredients. The Opadry II red 32K15441 film coating contains lactose monohydrate, HPMC 2910/Hypromellose 15cp, titanium dioxide, triacetin (glycerol triacetate), and red iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Refer to the outer packaging for the shelf life/expiry date of the product.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

INLYTA® tablets are supplied as follows:

1 mg tablets are red film-coated, oval tablets debossed with “Pfizer” on one side and “1 XNB” on the other; available in bottles of 180 and blister packs of 28 or 56 tablets.

5 mg tablets are red film-coated, triangular tablets debossed with “Pfizer” on one side and “5 XNB” on the other; available in bottles of 60 and blister packs of 28 or 56 tablets.

Not all pack sizes are marketed.

7. PRODUCT OWNER

Pfizer Inc.
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