SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

INLYTA® 1 mg film-coated tablets

INLYTA® 3 mg film-coated tablets

INLYTA® 5 mg film-coated tablets

INLYTA® 7 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each INLYTA 1 mg film-coated tablet contains 1 mg axitinib.

Each INLYTA 3 mg film-coated tablet contains 3 mg axitinib.

Each INLYTA 5 mg film-coated tablet contains 5 mg axitinib.

Each INLYTA 7 mg film-coated tablet contains 7 mg axitinib.

INLYTA film-coated tablets contain sugar.

Excipients with known effect

Each INLYTA 1 mg film-coated tablet contains 33,60 mg lactose monohydrate.

Each INLYTA 3 mg film-coated tablet contains 35,28 mg lactose monohydrate.

Each INLYTA 5 mg film-coated tablet contains 58,8 mg lactose monohydrate.

Each INLYTA 7 mg film-coated tablet contains 82,32 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

INLYTA 1 mg film-coated tablets are red, oval shaped and debossed with “Pfizer” on one side and “1 XNB” on the other.

INLYTA 3 mg film-coated tablets are red, round shaped and debossed with “Pfizer” on one side and “3 XNB” on the other.

INLYTA 5 mg film-coated tablets are red, triangular shaped and debossed with “Pfizer” on one side and “5 XNB” on the other.

INLYTA 7 mg film-coated tablets are red, diamond shaped and debossed with “Pfizer” on one side and “7 XNB” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INLYTA is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) with a clear cell component or advanced papillary cell renal carcinoma, after failure of previous systemic therapy and total nephrectomy of the involved kidney.

4.2 Posology and method of administration

Treatment with INLYTA should be conducted by a medical practitioner experienced in the use of anticancer therapies.

Posology

The recommended starting oral dose of INLYTA is 5 mg twice daily.

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 INLYTA 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 anti-hypertensive medication, may have their dose increased to 7 mg twice daily. Subsequently, using the same criteria, patients who tolerate the INLYTA 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 INLYTA therapy. When dose reduction is necessary, the INLYTA 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.

Special populations

Use in the elderly

No dose adjustment is required.

Hepatic impairment

No dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering INLYTA 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). INLYTA 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).

Paediatric population

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

Method of administration

INLYTA is for oral use.

INLYTA may be taken with or without food.

The film-coated tablets should be swallowed whole with a glass of water.

4.3 Contraindications

- Hypersensitivity to axitinib or any of the ingredients contained in INLYTA (listed in section 6.1).
- Pregnancy and lactation, and women of childbearing potential (see section 4.6).
- Children < 18 years of age (see section 4.2).
- Patients with evidence of untreated brain metastasis or recent gastrointestinal bleeding (see section 4.4).
- Severe hepatic impairment.
- History of recent (within the previous 12 months) arterial thromboembolism (myocardial infarction, stroke, transient ischaemic attack) when other appropriate treatment options are available (see section 4.4).
- History of recent (within the previous 6 months) venous thromboembolism (deep vein thrombosis, pulmonary embolism) when other appropriate treatment options are available (see section 4.4).
- Uncontrolled hypertension
- Uncontrolled cardiac failure
- Uncontrolled hypothyroidism
- A history of previous posterior reversible encephalopathy syndrome (PRES)
- A tendency to bleeding
- A recent history of a gastrointestinal perforation and/or fistula when other treatment options are available
- Unhealed surgery of trauma wounds

4.4 Special warnings and precautions for use

Cardiac failure events

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 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.

In the pivotal study hypertensive crisis was reported in 2/359 patients (< 1 %) receiving INLYTA. 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 treatment and blood pressure increases have been observed as early as 4 days after starting INLYTA. Discontinuation of INLYTA treatment due to hypertension may be necessary.

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 medicines, INLYTA should be stopped. If INLYTA is stopped, patients receiving anti-hypertensive medications should be monitored for hypotension.

Thyroid dysfunction

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.

In the pivotal study hyperthyroidism was reported in 4/359 patients (1 %) receiving INLYTA. 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.

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 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 the pivotal study the most frequent arterial thromboembolic event was transient ischaemic attack (1 %). Fatal cerebrovascular accident was reported in < 1 % of patients receiving INLYTA.

In monotherapy studies with INLYTA, arterial thromboembolic events (including transient ischaemic 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 (see section 4.3).

Venous thromboembolic events

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 %). Grade 3/4 venous thromboembolic events included pulmonary embolism, deep vein thrombosis and retinal vein occlusion/thrombosis. 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 (see section 4.3).

Elevation of haemoglobin or haematocrit

Increases in haemoglobin or haematocrit, reflective of increases in red blood cell mass, may occur during treatment with INLYTA. An increase in red blood cell mass may increase the risk of thromboembolic events.

Elevated haemoglobin above the upper limit of normal (ULN) was observed in 31/320 patients (10 %) receiving INLYTA.

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

Haemorrhage

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

In the pivotal study the most common haemorrhagic events in patients treated with INLYTA were epistaxis (6 %), haematuria (3 %), haemoptysis (2 %), and rectal haemorrhage (2 %). Grade 3/4 haemorrhagic events were reported in 5/359 patients (1 %) receiving INLYTA (including cerebral haemorrhage, haematuria, haemoptysis, lower gastrointestinal haemorrhage, and melaena). Fatal haemorrhage was reported in 1/359 patients (< 1 %) receiving INLYTA (gastric haemorrhage).

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 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. A case of fatal gastrointestinal perforation has been reported in a monotherapy study.

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

Wound healing complications

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 pooled clinical studies with INLYTA for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (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. Grade 3 proteinuria was reported in 11/359 patients (3 %) receiving INLYTA.

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 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).

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).

Lactose intolerance

INLYTA contains lactose. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take INLYTA.

4.5 Interaction with other medicines and other forms of interaction

In vitro data indicate that INLYTA is metabolised 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 INLYTA 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 INLYTA plasma concentrations. Grapefruit may also increase INLYTA 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 INLYTA is recommended.

CYP3A4/5 inducers

Rifampicin, 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 INLYTA in healthy volunteers.

Co-administration of INLYTA with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbitone, and *Hypericum perforatum (*[also known as St. John's wort]) may decrease INLYTA 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 INLYTA is recommended.

In vitro studies of CYP and UGT inhibition and induction

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

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

In vitro studies also indicated that INLYTA has the potential to inhibit CYP2C8.
However, co-administration of INLYTA 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 INLYTA does not induce CYP1A1, CYP1A2, or CYP3A4/5, therefore co-administration of INLYTA 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 INLYTA 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

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving INLYTA. They should use adequate contraception.

Women of childbearing potential must use effective contraception during and up to 1 week after treatment.

Pregnancy

INLYTA is contraindicated during pregnancy (see section 4.3).

Breastfeeding

Women taking INLYTA should not breastfeed their infants (see section 4.3).

Fertility

Based on non-clinical findings, INLYTA has the potential to impair reproductive function and fertility in men and women.

Conservation of sperm or ova should be considered before initiation of treatment with INLYTA.

4.7 Effects on ability to drive and use machines

Patients should be advised that they may experience events such as dizziness and/or fatigue during treatment with INLYTA. Such symptoms may impair their ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common (≥ 20 %) adverse reactions observed following treatment with INLYTA were diarrhoea, hypertension, fatigue, decreased appetite, nausea, weight decreased, dysphonia, palmar-plantar erythrodysaesthesia (hand-foot) syndrome, haemorrhage, hypothyroidism, vomiting, proteinuria, cough, and constipation.

Tabulated list of adverse reactions

The data described below reflect exposure to INLYTA in 672 patients with advanced RCC who participated in the pivotal randomised clinical study or 4 additional studies with INLYTA in patients with RCC.

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 patients with advanced RCC who received INLYTA

System organ class	**Frequency category**	**Adverse reaction**	**INLYTA (N=672) frequency**		
			All Grades %	**Grade 3 %**	**Grade 4 %**
Blood and lymphatic system disorders	Common	Anaemia	6,3	1,2	0,4
		Polycythaemia	1,5	0,1	0
Endocrine disorders	Very common	Hypothyroidism	24,6	0,3	0
	Common	Hyperthyroidism	1,6	0,1	0,1
Metabolism and nutrition disorders	Very common	Decreased appetite	39,0	3,6	0,3
	Common	Dehydration	6,7	3,1	0,3
		Hyperkalaemia	2,7	1,2	0,1
		Hypercalcaemia	2,2	0,1	0,3

Nervous system disorders	Very common	Headache Dysgeusia	16,2 11,5	0,7 0	0 0
	Common	Dizziness	9,1	0,6	0
	Un-common	Reversible posterior leukoencephalopathy syndrome (RPLS)	0,3	0,1	0
Ear and labyrinth disorders	Common	Tinnitus	3,1	0	0
Cardiac disorders	Common	Cardiac failure events	1,8	0,3	0,7
Vascular disorders	Very common	Hypertension Haemorrhage	51,2 25,7	22,0 3,0	1,0 1,0
	Common	Venous thromboembolic events Arterial thrombotic events	2,8 2,8	0,9 1,2	1,2 1,3
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea Cough Dysphonia	17,1 20,4 32,7	3,6 0,6 0	0,6 0 0,1

Gastro-intestinal disorders	Very common	Diarrhoea	55,4	10,1	0,1
		Vomiting	23,7	2,7	0,1
		Nausea	33,0	2,2	0,1
		Abdominal pain	14,7	2,5	0,3
		Stomatitis	15,5	1,8	0
		Constipation	20,2	1,0	0
		Dyspepsia	11,2	0,1	0
	Common	Upper abdominal pain	9,4	0,9	0
		Haemorrhoids	3,3	0	0
		Glossodynia	2,8	0	0
		Gastrointestinal perforation and fistula	1,9	0,9	0,3
Hepatobiliary disorders	Common	Hyper-bilirubinaemia	1,3	0,1	0,1
Skin and sub-cutaneous tissue disorders	Very common	Palmar-plantar eryth-rodysaesthesia (hand-foot syndrome)	32,1	7,6	0
		Rash	14,3	0,1	0
		Dry skin	10,1	0,1	0
	Common	Erythema	3,7	0	0
		Pruritus	6,0	0	0
		Alopecia	5,7	0	0
Musculo-skeletal and connective	Very common	Arthralgia	17,7	1,9	0,3
		Pain in extremity	14,1	1,0	0,3
	Common	Myalgia	8,2	0,6	0,1

tissue disorders					
Renal and urinary disorders	Very common	Proteinuria	21,1	4,8	0,1
General disorders and adminis-tration site conditions	Very common	Fatigue Asthenia Mucosal inflammation	45,1 13,8 13,7	10,6 2,8 1,0	0,3 0,3 0
Investi-gations	Very common	Decreased weight	32,7	4,9	0
	Common	Increased lipase Increased blood creatinine Increased alanine aminotransferase Increased blood alkaline phosphatase Increased aspartate aminotransferase Increased amylase	3,7 5,7 6,5 4,8 6,1 3,4	0,7 0,4 1,2 0,3 1,0 0,6	0,7 0 0 0 0 0,4

Post-marketing experience

The following adverse reactions have been identified during post-approval use of INLYTA:

System organ class	Adverse reaction
Cardiac disorders	Cardiac failure event
Gastrointestinal disorders	Glossodynia

Reporting of suspected adverse reactions

Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com

4.9 Overdose

The symptoms of an overdose may include hypertension, seizures associated with hypertension, and fatal haemoptysis. In cases of suspected overdose, INLYTA should be withheld and supportive care instituted. There is no specific treatment for INLYTA overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors. ATC code: L01EK01.

Mechanism of action

Axitinib is a tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to inhibit VEGF-mediated endothelial cell proliferation and survival.

Clinical efficacy and safety

Summary of clinical studies

The safety and efficacy of axitinib were evaluated in a randomised, open-label, multicentre Phase 3 study. Patients (n=723) with advanced RCC whose disease had progressed on or after treatment with one prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomised (1:1) to receive axitinib (n=361) or sorafenib (n=362).

Of the patients enrolled in this study, 389 patients (54 %) had received one prior sunitinib-based therapy, 251 patients (35 %) had received one prior cytokine-based therapy (interleukin-2 or interferon-alfa), 59 patients (8 %) had received one prior bevacizumab-based therapy, and 24 patients (3 %) had received one prior temsirolimus-based therapy.

There was a statistically significant advantage for axitinib over sorafenib for the progression-free survival (PFS) (see Table 2 and Figure 1).

There was no statistically significant difference between the arms in overall survival (OS).

Table 2. Efficacy results by independent assessment

Endpoint/study population	**Axitinib**	**Comparator (sorafenib)**	**HR (95 % CI)**	**P-value**
PFS [a,b]				
Overall ITT	n= 361	n = 362		
Median, months	6,7	4,7	0,67	< 0,0001[c]
(95 % CI)	(6,3, 8,6)	(4,6, 5,6)	(0,54, 0,81)	
Sunitinib-refractory subgroup	n=194	n=195		
Median, months	4,8	3,4	0,74	0,0107[d]
(95 % CI)	(4,5, 6,4)	(2,8, 4,7)	(0,57, 0,96)	
Cytokine-refractory subgroup	n=126	n=125		
Median, months	12,1	6,5	0,46	< 0,0001[d]
(95 % CI)	(10,1, 13,9)	(6,3, 8,3)	(0,32, 0,68)	

OS				
Median, months	20,1	19,2	0,97	0,374[e]
(95 % CI)	(16,7, 23,4)	(17,5, 22,3)	(0,80, 1,17)	
ORR	n=361	n=362		
% (95 % CI)	19,4	9,4	2,06[f]	0,0001[g]
	(15,4, 23,9)	(6,6, 12,9)	(1,41, 3,00)	

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

[a] Time from randomisation 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).

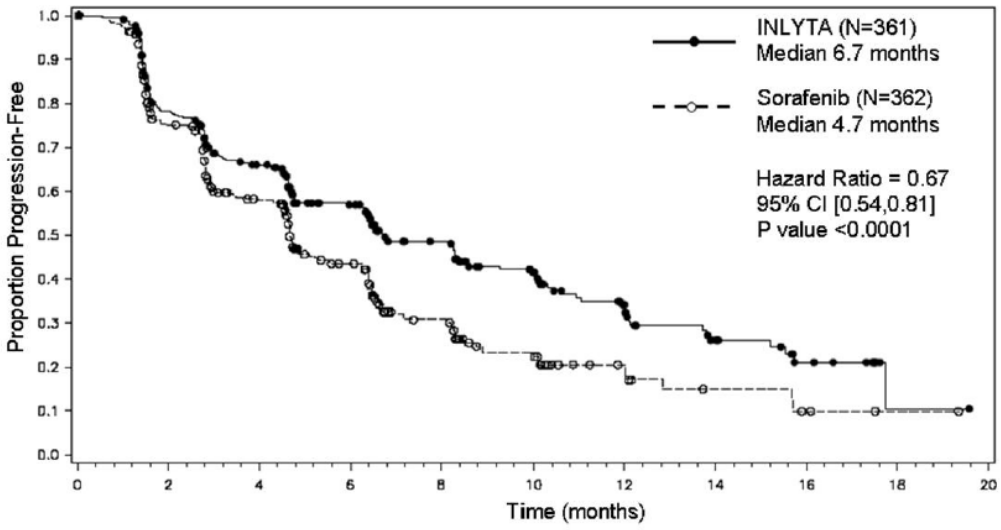
[d] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

[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; 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 %.

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 renal cell carcinoma (RCC). The geometric mean oral clearance and apparent volume of distribution were 38 L/h and 160 L, respectively.

Metabolism and elimination

Axitinib is metabolised 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 faeces and 23 % of the radioactivity was recovered in urine.

Unchanged axitinib, accounting for 12 % of the dose, was the major component identified in faeces. 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

Hepatic impairment

In vitro and *in vivo* data indicate that axitinib is primarily metabolised 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.

Paediatric population

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

5.3 Preclinical safety data

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 ≥ 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 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 (≥ 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 foetal 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose

Lactose monohydrate

Croscarmellose sodium

Magnesium stearate

Tablet film-coating

Hypromellose

Titanium dioxide

Lactose monohydrate

Triacetin

Red iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blisters in the carton until required for use.

Keep the bottles tightly closed.

Protect from light.

6.5 Nature and contents of container

INLYTA 1 mg film-coated tablets: 60 mL or 120 mL white HDPE bottles containing desiccant with induction seal and child-resistant white polypropylene closures containing 60, 90 or 180 tablets respectively. Cartons containing aluminium foil blisters with aluminium foil backing of 14 tablets per blister strip, in pack sizes of 28 or 56 tablets.

INLYTA 3 mg film-coated tablets: 60 mL and 120 mL white HDPE bottles containing desiccant with induction seal and child-resistant white polypropylene closures containing 60, 90 or 180 tablets respectively. Cartons containing aluminium foil blisters with aluminium foil backing of 14 tablets per blister strip, in pack sizes of 28 or 56 tablets.

INLYTA 5 mg film-coated tablets: 60 mL and 180 mL white HDPE bottles containing desiccant with induction seal and child-resistant white polypropylene closures containing 60, 90 or 180 tablets respectively. Cartons containing aluminium foil blisters with aluminium foil backing of 14 tablets per blister strip, in pack sizes of 28 or 56 tablets.

INLYTA 7 mg film-coated tablets: 60 mL and 325 mL white HDPE bottles containing desiccant with induction seal and child-resistant white polypropylene closures containing 60, 90 or 180 tablets respectively. Cartons containing aluminium foil blisters with aluminium foil backing of 14 tablets per blister strip, in pack sizes of 28 or 56 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

INLYTA 1 mg: **48/26/0605**

INLYTA 3 mg: **48/26/0606**

INLYTA 5 mg: **48/26/0607**

INLYTA 7 mg: **48/26/0608**

9. DATE OF FIRST AUTHORISATION

19 May 2020

10. DATE OF REVISION OF THE TEXT

01 July 2025

Manufacturer:

Pfizer Manufacturing Deutschland GmbH, Freiburg Im Breisgau, Germany