INLYTA® (axitinib) tablets **Fact Sheet**

PRODUCT DESCRIPTION	INLYTA, a kinase inhibitor, is an oral therapy that selectively inhibits vascular endothelial growth factor (VEGF) receptors 1, 2 and 3, which are receptors that can influence tumour growth, vascular angiogenesis, and progression of cancer (the spread of tumours).[1]
INDICATIONS	INLYTA has been granted marketing authorisation by the European Medicines Agency (EMA) for use in the EU in adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.[2] INLYTA's approval is based on data from the Phase III (AXIS) trial which demonstrated that INLYTA significantly extended progression free survival (PFS) [HR=0.67, 0.56-0.81; P<0.0001], the primary endpoint of the study, with a median PFS of 6.8 months (95% CI: 6.4, 8.3) compared with 4.7 months (95% CI: 4.6, 6.3) for those treated with sorafenib, a current standard of care in second-line advanced RCC. This represents a 45 percent improvement in median PFS compared to sorafenib.[2]
ABOUT VEGF RECEPTORS	VEGF receptors 1, 2 and 3 can influence tumour growth, vascular angiogenesis, and progression of cancer (the spread of tumours).[3] Preclinical evidence suggests that inhibiting all three VEGF receptor signaling pathways may more efficiently disrupt tumour growth, vascular angiogenesis, and metastatic progression of cancer through lymphangiogenesis, than by inhibiting an individual pathway.[3] INLYTA is a selective and potent inhibitor of VEGFR-1, 2 and 3, targeting these with potency in the picomolar range.[3,4]
CLINICAL STUDIES	The following INLYTA (axitinib) studies are ongoing: • AGILE 1051 (A4061051, NCT00920816): A randomised, Phase III clinical trial evaluating the efficacy and safety of axitinib in patients with treatment-naïve as well as previously treated advanced RCC.[5] • AGILE 1046 (A4061046, NCT00835978): A randomised, double-blind, Phase II study investigating axitinib with or without dose titration in patients with metastatic renal cell carcinoma.[6] o Additional objectives include an assessment of correlations with clinical outcome and/or blood pressure measurements in patients receiving axitinib with or without dose titration. An additional trial of INLYTA, as a treatment for advanced hepatocellular carcinoma (HCC), is currently open and enrolling: • AGILE 1058 (A4061046, NCT01210495): A randomised, double-blind Phase II study of axitinib plus best supportive care versus placebo plus best supportive care in patients with advanced HCC following failure of one prior antiangiogenic therapy.[7]
PATIENT ACCESS TO INLYTA	Pfizer strongly believes patients should have access to medications they need, and has established reimbursement support services and patient assistance programs for them. Pfizer is committed to helping eligible patients whose physician recommends INLYTA gain access to the medication.

IMPORTANT SAFETY INFORMATION ABOUT INLYTA[2]	**Important Safety Information About INLYTA (axitinib)[2]** The most common (≥20%) adverse events (AEs) occurring in patients receiving INLYTA (all grades) were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot syndrome, weight decreased, vomiting, asthenia, and constipation. The most common (≥10%) grade 3/4 AEs occurring in patients receiving INLYTA were hypertension, diarrhea, and fatigue. The most common (≥20%) lab abnormalities occurring in patients receiving INLYTA (all grades) included increased creatinine, decreased bicarbonate, hypocalcemia, decreased hemoglobin, decreased lymphocytes (absolute), increased ALP, hyperglycemia, increased lipase, increased amylase, increased ALT, and increased AST. **POSOLOGY AND METHOD OF ADMINISTRATION[2]** The recommended starting dose of INLYTA is 5 mg twice daily approximately 12 hours apart with or without food. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs that cannot be managed by concomitant medicinal products or dose adjustments. 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 increase or reduction is recommended based on individual safety and tolerability. **SPECIAL WARNINGS AND PRECAUTIONS OF USE[2]** **Hypertension** In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypertension was very commonly reported. 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. 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 medicinal products, the INLYTA dose should be reduced. For patients who develop severe hypertension, temporarily interrupt INLYTA and restart at a lower dose once the patient is normotensive. If INLYTA is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension. In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome a diagnostic brain magnetic resonance image (MRI) should be considered. **Arterial embolic and thrombotic events** In clinical studies with INLYTA, arterial embolic and thrombotic events (including transient ischemic attack, myocardial infarction, cerebrovascular accident and retinal artery occlusion) were reported and can be fatal. 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 embolic or thrombotic event within the previous 12 months. **Venous embolic and thrombotic events** In clinical studies with INLYTA, venous embolic and thrombotic events (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis) were reported. 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 embolic and thrombotic event within the previous 6 months. Arterial and venous thrombotic events have been observed and can be fatal.

Haemorrhage
In clinical studies with INLYTA, haemorrhagic events, including fatal events, were reported.

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 clinical studies with INLYTA, events of gastrointestinal perforation and fistulas, including death, were reported.

Symptoms of gastrointestinal perforation or fistula should be periodically monitored for 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.

Posterior reversible encephalopathy syndrome
In clinical studies with INLYTA, events of posterior reversible encephalopathy syndrome (PRES) were reported.

PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with signs or symptoms of PRES, temporarily interrupt or permanently discontinue INLYTA treatment. The safety of reinitiating INLYTA therapy in patients previously experiencing PRES is not known.

Proteinuria
In clinical studies with INLYTA, proteinuria, including that of Grade 3 severity, was reported.

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.

Liver-related adverse events
In a controlled clinical study with INLYTA for the treatment of patients with RCC, liver-related events were reported. The most commonly reported liver-related adverse reactions included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin. No concurrent elevations of ALT (> 3 times the upper limit of normal [ULN]) and bilirubin (> 2 times the ULN) were observed.

In a clinical dose-finding study, concurrent elevations of 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).

Liver function tests should be monitored before initiation of, and periodically throughout, treatment with INLYTA.

	Hepatic impairment In clinical studies with INLYTA, the systemic exposure to INLYTA was approximately two-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) and should not be used in this population. **Elderly patients (≥ 65 years) and race** In a controlled clinical study with INLYTA for the treatment of patients with RCC, 34% of patients treated with INLYTA were ≥ 65 years of age. The majority of patients were White (77%) or Asian (21%). Although greater sensitivity to develop adverse reactions in some older patients and Asian patients cannot be ruled out, overall, no major differences were observed in the safety and effectiveness of INLYTA between patients who were ≥ 65 years of age and non-elderly, and between White patients and patients of other races. No dosage adjustment is required on the basis of patient age or race. **Lactose** This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. **Women of childbearing potential** Women of childbearing potential should be advised of potential hazard to the foetus and to avoid becoming pregnant while receiving INLYTA. INLYTA should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicinal product. **CYP3A4/5 inhibitors and inducers** Avoid strong CYP3A4/5 inhibitors. If unavoidable, reduce INLYTA dose. Avoid strong CYP3A4/5 inducers and, if possible, avoid moderate CYP3A4/5 inducers. Please see the INLYTA (axitinib) Summary of Product Characteristics for more information.

For more information, please visit www.pfizercancertrials.com or www.clinicaltrials.gov or contact

References

[1] Rini B, Escudier B et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial The Lancet, Volume 378, Issue 9807, Pages 1931 - 1939, 3 December 2011 doi:10.1016/S0140-6736(11)61613-9

[2] Summary of Product Characteristics for INLYTA®. Sandwich, Kent: UK; 2012

[3] Hu-Lowe DD et al. Nonclinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. Clin Cancer Res 2008; 14:7272–7283

[4] Escudier B, Gore M. Axitinib for the management of metastatic renal cell carcinoma. Drugs R D 2011; 11:113–126]

[5] ClinicalTrials.gov. Axitinib (AG-013736) For the Treatment of Metastatic Renal Cell Cancer. http://www.clinicaltrials.gov/ct2/show/NCT00920816?term=A4061051&rank=1

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[7] Clinical Trials.gov. Axitinib For The Treatment of Advanced Hepatocellular Carcinoma. Available at: http://clinicaltrials.gov/ct2/show/NCT01210495?term=axitinib&rank=21. Accessed February 28, 2012.