### INDICATION

INLYTA® (axitinib) is a kinase inhibitor and in the United States is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.¹

### MECHANISM OF ACTION

Vascular endothelial growth factor, or VEGF, plays an important role in RCC angiogenesis where it is constitutively upregulated.²³⁴⁵

VEGF acts on three receptors, VEGFR-1, VEGFR-2, and VEGFR-3.⁶ These receptors are implicated in pathologic angiogenesis, tumor growth and cancer progression.¹

INLYTA has been shown to inhibit receptor tyrosine kinases including VEGFR-1, -2, and 3.¹

Preclinical evidence suggests that VEGF continues to play a role in tumor growth, even after progression on systemic therapy.⁷⁸⁹

However, preclinical activity does not necessarily correlate with clinical outcomes.

### KIDNEY CANCER STUDY (AXIS TRIAL)

The approval of INLYTA was based on data from the AXIS trial – a Phase 3 randomized, open-label, multicenter head-to-head study with sorafenib.¹

- Patients (N=723) with metastatic 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).

- 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.

- INLYTA significantly extended progression-free survival (PFS) [HR=0.67, 0.54-0.81; P<0.0001] with a median PFS of 6.7 months (95% CI: 6.3, 8.6) compared with 4.7 months (95% CI: 4.6, 5.6) for those treated with sorafenib, a standard of care for this patient population, representing a 43 percent improvement in median PFS compared to sorafenib.

### IMPORTANT SAFETY INFORMATION

Hypertension including hypertensive crisis has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported. INLYTA has not been studied in patients with 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.

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of
cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on wound healing have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. If signs or symptoms occur, permanently discontinue treatment.

Monitor for proteinuria before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate hepatic impairment, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

Women of childbearing potential should be advised of potential hazard to the fetus and to avoid becoming pregnant while receiving INLYTA.

Avoid strong CYP3A4/5 inhibitors. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong CYP3A4/5 inducers and, if possible, avoid moderate CYP3A4/5 inducers.

The most common (≥20%) adverse events (AEs) occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

The most common (≥10%) grade 3/4 AEs occurring in patients receiving INLYTA (vs sorafenib) were hypertension (16% vs 11%), diarrhea (11% vs 7%), and fatigue (11% vs 5%).

The most common (≥20%) lab abnormalities occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine (55% vs 41%), decreased bicarbonate (44% vs 43%), hypocalcemia (39% vs 59%), decreased hemoglobin (35% vs 52%), decreased lymphocytes (absolute) (33% vs 36%), increased ALP (30% vs 34%), hyperglycemia (28% vs 23%), increased lipase (27% vs 46%), increased amylase (25% vs 33%), increased ALT (22% vs 22%), and increased AST (20% vs 25%).

Please see full Prescribing Information for INLYTA.

**PATIENT ACCESS TO INLYTA**

Commercially insured patients may be eligible to use the Pfizer Co-Pay One Savings Card when INLYTA is prescribed and pay no more than $10 out-of-pocket monthly for their medication (Limits, terms, and conditions apply).

Patients who participate in federal or state healthcare programs, such as Medicaid or Medicare, are not eligible for the Pfizer Co-Pay One Savings Card. These patients can call
Pfizer RxPathways™, and a counselor will work with them to research alternate funding options and help with application processes. If alternate funding cannot be secured, patients who meet eligibility requirements can receive their Pfizer medicine for free through the patient assistance program. Call 1-866-706-2400 or visit www.PfizerRxPath.com for more information.

Access to medicines is a cornerstone of Pfizer’s commitment to health care. For more than 25 years, Pfizer has offered an array of prescription assistance programs to help eligible patients get access to their Pfizer medicines. Today, this assistance is provided through Pfizer RxPathways, which helps eligible patients get access to their Pfizer medicines by offering a range of support services, including insurance counseling, co-pay help, providing Pfizer medicines for free or at a savings, and more.

Pfizer’s patient assistance programs have helped millions of uninsured and underinsured patients gain access to the medications they need. For more information on Pfizer RxPathways, please visit www.PfizerRxPath.com.

CONTACT INFORMATION & ADDITIONAL INFORMATION

If you are interested in speaking with a Pfizer Oncology representative, please contact Sally Beatty at Sally.Beatty@pfizer.com or (212) 733-6566.

For information about INLYTA clinical trials currently enrolling in their area, patients and their physicians are encouraged to call Pfizer Oncology’s toll-free information line at 1-800-718-1021 (U.S.) or visit www.pfizercancertrials.com.

INLYTA® (axitinib) tablets for oral administration
Initial U.S. Approval: 2012

1 INDICATIONS AND USAGE

INLYTA is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy. (1)

The starting dose is 5 mg orally twice daily. Dose adjustments can be made based on individual safety and tolerability. (2.1, 2.2)

Administer INLYTA dose approximately 12 hours apart with or without food. (2.1)

INLYTA should be swallowed whole with a glass of water. (2.1)

If a strong CYP3A4/5 inhibitor is required, decrease the INLYTA dose by approximately half. (2.2)

Permanent discontinuation INLYTA is recommended when CYP3A4/5 inhibitors are co-administered. (7.2)

Dosage increase or reduction is recommended based on individual safety and tolerability. (2.2, 5.12)

6 ADVERSE REACTIONS

The most common (≥20%) adverse reactions are diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, anemia, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Avoid strong CYP3A4/5 inhibitors. (7.2)

Avoid strong CYP3A4/5 inducers. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

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Sections or subsections omitted from the Full Prescribing Information are not listed.
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. Use INLYTA 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 12 months.

5.3 Venous Thromboembolic Events

In clinical trials, venous thromboembolic events have been reported, including deaths. In a randomized 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, retinal vein occlusion and retinal vein thrombosis) and 2/355 patients (1%) receiving sorafenib. Fatal cerebrovascular accident was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical trials with INLYTA, venous thromboembolic events were reported in 11/359 patients (3%) receiving INLYTA and 2/355 patients (1%) receiving sorafenib. Grade 3/4 cardiac failure was observed in 2/359 patients (1%) receiving INLYTA and none of the patients receiving sorafenib. Grade 3/4 pulmonary embolism was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. Fatal pulmonary embolism was reported in 1/359 patients (<1%). Grade 3/4 hypertension was observed in 2/359 patients (1%) receiving INLYTA and 1/355 patients (<1%) receiving sorafenib. In clinical trials with INLYTA, hypertension was managed with standard antihypertensive therapy. Discontinuation of INLYTA treatment due to hypertension occurred in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib [see Adverse Reactions (6.1)].

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, reduce the INLYTA dose. Discontinue INLYTA if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis. If INLYTA is interrupted, patients on anti-hypertensive medications should be monitored for hypertension [see Dosage and Administration (2.2)].

5.4 Hemorrhage

In a controlled clinical study with INLYTA for the treatment of patients with RCC, hemorrhagic events were reported in 58/359 patients (16%) receiving INLYTA and 64/355 patients (18%) receiving sorafenib. Grade 3/4 hemorrhagic events were reported in 5/359 (1%) patients receiving INLYTA (including cerebral hemorrhage, hematoma, hemoptysis, lower gastrointestinal hemorrhage, and melena) and 11/355 (3%) patients receiving sorafenib. Fatal hemorrhage was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical trials with INLYTA, venous thromboembolic events were reported in 22/715 patients (3%), with two deaths secondary to cerebrovascular accident.

Use INLYTA 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.

5.5 Cardiac Failure

In a controlled clinical study with INLYTA for the treatment of patients with RCC, cardiac failure was reported in 6/359 patients (2%) receiving INLYTA and 3/355 patients (1%) receiving sorafenib. Grade 3/4 cardiac failure was observed in 2/359 patients (1%) receiving INLYTA and 1/355 patients (<1%) receiving sorafenib. Fatal cardiac failure was reported in 2/359 patients (1%) receiving INLYTA and 2/355 patients (<1%) receiving sorafenib. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The safety of INLYTA has been evaluated in 715 patients in monotherapy studies, which included 537 patients with advanced RCC. The data described [see Adverse Reactions (6.1)] were observed in patients with advanced RCC who participated in a randomized clinical study versus sorafenib [see Clinical Studies (14)].

The following risks, including appropriate action to be taken, are discussed in greater detail in other sections of the label [see Warnings and Precautions (5.1-5.13), Hypertension, arterial thromboembolic events, venous thromboembolic events, hemorrhage, cardiac failure, gastrointestinal perforation and fistula formation, thyroid dysfunction, wound healing complications, RPLS, proteinuria, elevation of liver enzymes, hepatic impairment and fetal development.

6.1 Clinical Trials Experience

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 499/359 patients (55%) receiving INLYTA and 229/355 patients (62%) receiving sorafenib. Permanent discontinuation due to an adverse reaction occurred in 34/359 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. Table 1 presents adverse reactions reported in ≥10% patients who received INLYTA or sorafenib.
7.1 CYP3A4/5 Inhibitors

Co-administration of ketoconazole, a strong inhibitor of CYP3A4/5, increased the plasma exposure of axitinib in healthy volunteers. Co-administration of INLYTA with strong CYP3A4/5 inhibitors 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, the INLYTA dose should be reduced [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

7.2 CYP3A4/5 Inducers

Co-administration of rifampin, a strong inducer of CYP3A4/5, reduced the plasma exposure of axitinib in healthy volunteers. Co-administration of INLYTA with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John’s wort) should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]. Moderate CYP3A4/5 inducers (e.g., bosantan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should be avoided if possible.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.13)].

There are no adequate and well-controlled studies with INLYTA in pregnant women. INLYTA can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Axitinib was teratogenic, embryotoxic and fetotoxic in mice at exposures lower than human exposures at the recommended starting dose. 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.

Oral axitinib administered twice daily to female mice prior to mating and throughout the first week of pregnancy caused an increase in post-implantation loss at all doses tested (~15 mg/kg/dose, approximately 10 times the systemic exposure [AUC] in patients at the recommended starting dose). In an embryo-fetal developmental toxicity study, pregnant mice received oral doses of 0.15, 0.5 and 1.5 mg/kg/dose axitinib twice daily during the period of organogenesis. Embryo-fetal toxicities observed in the absence of maternal toxicity included malformation (cleft palate) at 1.5 mg/kg/dose (approximately 0.5 times the AUC in patients at the recommended starting dose) and variation in skeletal ossification at ~0.5 mg/kg/dose (approximately 0.15 times the AUC in patients at the recommended starting dose).

8.3 Nursing Mothers

It is not known whether axitinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INLYTA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of INLYTA in pediatric patients have not been studied.

Toxicities in bone and teeth were observed in immature mice and dogs administered oral axitinib twice daily for 1 month or longer. Effects in bone consisted of thickened growth plates in mice and dogs at ~6 times and ~15 times, respectively, the systemic exposure [AUC] in patients at the recommended starting dose. Abnormalities in growing incisor teeth (including dental caries, malocclusions and broken and/or missing teeth) were observed in mice administered oral axitinib twice daily at ~5 mg/kg/dose (approximately 1.5 times the AUC in patients at the recommended starting dose). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

8.5 Geriatric Use

In a controlled clinical study with INLYTA for the treatment of patients with RCC, 123/359 patients (34%) treated with INLYTA were ≥65 years of age. Although greater sensitivity in some older individuals cannot be ruled out, no overall differences were observed in the safety and effectiveness of INLYTA between patients who were ≥65 years of age and younger.

No starting dose adjustment is required in elderly patients [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

8.6 Hepatic Impairment

In a dedicated hepatic impairment trial, compared to subjects with normal hepatic function, systemic exposure following a single dose of INLYTA was similar in subjects with baseline mild hepatic impairment (Child-Pugh class A) and higher in subjects with baseline moderate hepatic impairment (Child-Pugh class B).

No starting dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). A starting dose decrease is recommended when administering INLYTA to patients with moderate hepatic impairment (Child-Pugh class B) [see Dosage and Administration (2.2), Warnings and Precautions (5.12), and Clinical Pharmacology (12.3)].

INLYTA has not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

8.7 Renal Impairment

No dedicated renal impairment trial for axitinib has been conducted. Based on the population pharmacokinetic analyses, no significant difference in axitinib clearance was observed in patients with pre-existing mild to severe renal impairment (15 mL/min ≤creatinine clearance [CLcr] <89 mL/min) [see Clinical Pharmacology (12.3)]. No starting dose adjustment is needed for patients with pre-existing mild to severe renal impairment. Caution should be used in patients with end-stage renal disease (CLcr <15 mL/min).

10 OVERDOSAGE

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).

### Table 1. Adverse Reactions Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>INLYTA (N=359)</th>
<th>Sorafenib (N=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3/4</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>23</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>Thrombo-angiitis</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>Weight increased</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Anorexia</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Cough</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
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<td>12</td>
</tr>
<tr>
<td>Antralgia</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Dysthnia</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Rash</td>
<td>13</td>
<td>32</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Dry skin</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10</td>
<td>2</td>
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<tr>
<td>Pruritus</td>
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<td>12</td>
</tr>
<tr>
<td>Alopecia</td>
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<td>32</td>
</tr>
<tr>
<td>Chytridema</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

### Table 2. Laboratory Abnormalities Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>INLYTA (N=359)</th>
<th>Sorafenib (N=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades†</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32/1</td>
<td>35 &lt;1</td>
</tr>
<tr>
<td>Lymphocytes (absolute) decreased</td>
<td>317</td>
<td>33 &lt;3</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>312</td>
<td>15 &lt;1</td>
</tr>
<tr>
<td>White blood cells decreased</td>
<td>320</td>
<td>11 &lt;1</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>346</td>
<td>55 &gt;0</td>
</tr>
<tr>
<td>Bilirubin decreased</td>
<td>314</td>
<td>44 &lt;1</td>
</tr>
<tr>
<td>Hypocalemia</td>
<td>336</td>
<td>39 &gt;1</td>
</tr>
<tr>
<td>ALP increased</td>
<td>336</td>
<td>30 &gt;1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>336</td>
<td>28 &gt;2</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>336</td>
<td>27 &gt;5</td>
</tr>
<tr>
<td>Alanine increased</td>
<td>336</td>
<td>26 &gt;2</td>
</tr>
<tr>
<td>ALT increased</td>
<td>331</td>
<td>22 &gt;1</td>
</tr>
<tr>
<td>AST increased</td>
<td>331</td>
<td>20 &gt;1</td>
</tr>
<tr>
<td>Hypermaturemia</td>
<td>336</td>
<td>17 &gt;1</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>336</td>
<td>15 &lt;1</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>336</td>
<td>15 &lt;1</td>
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<td>336</td>
<td>13 &lt;4</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>336</td>
<td>13 &lt;2</td>
</tr>
</tbody>
</table>

† National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

Selected adverse reactions (all grades) that were reported in <10% of patients treated with INLYTA included dizziness (9%), upper abdominal pain (8%), myalgia (7%), dehydration (6%), epistaxis (6%), anemia (4%), hemorrhoids (4%), hematuria (3%), tinnitus (3%), increased AST (3%), glossodynia (3%), pulmonary embolism (2%), rectal hemorrhage (2%), hemoptysis (2%), deep vein thrombosis (1%), retinal-vein occlusion/thrombosis (1%), polycythemia (1%), and transient ischemic attack (1%).

Table 2 presents the most common laboratory abnormalities reported in ≥10% patients who received INLYTA or sorafenib.

**In vitro data indicate that axitinib is metabolized primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UDT) 1A1.**
In a clinical dose finding study with INLYTA, subjects 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.

11 DESCRIPTION

INLYTA (axitinib) is a kinase inhibitor. Axitinib has the chemical name N-methyl-2-[3-[(E)-2-pyrilinyl-2-vilnyl]-1H-indazol-6-ylsulfanyl]-benzamide. The molecular formula is C_{22}H_{18}N_{4}O_{3}S and the molecular weight is 386.47 Daltons. The chemical structure is:

![Chemical Structure of Axitinib]

Axitinib is a white to light-yellow powder with a pka of 4.8. The solubility of axitinib in aqueous media over the range pH 1.1 to pH 7.8 is in excess of 0.2 μg/mL. The partition coefficient (n-octanol/water) is 3.5.

INLYTA is supplied as red, film-coated tablets containing one mg or 5 mg of axitinib together with microcrystalline cellulose, lactose monohydrate, crossmelllose 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Axitinib has been shown to inhibit receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. VEGF-mediated endothelial cell proliferation and survival were inhibited by axitinib in vitro and in mouse models. Axitinib was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in tumor xenograft mouse models.

12.2 Pharmacodynamics

The effect of a single oral dose of INLYTA (5 mg) in the absence and presence of 400 mg ketoconazole on the QTc interval was evaluated in a randomized, single-blinded, 2:1 dose group crossover study in 35 healthy subjects. No large changes in mean QTc interval (i.e., >20 ms) from placebo were detected up to 3 hours post-dose. However, small increases in mean QTc interval (i.e., <10 ms) cannot be ruled out.

12.3 Pharmacokinetics

The population pharmacokinetic analysis pooled data from 17 trials in healthy subjects and patients with cancer. A two-compartment disposition model with first-order absorption and lag-time adequately describes the axitinib concentration-time profile.

Absorption and Distribution: Following single oral 5-mg dose administration, the mean C_{max} ranged from 2.5 to 4.1 hours. Based on the plasma half-life, steady state is expected within 2 to 3 days of dosing. Dosing of axitinib at 5 mg twice daily resulted in approximately 1.4-fold accumulation compared to administration of a single dose. At steady state, axitinib exhibits approximately linear pharmacokinetics within the 1-mg to 20-mg dose range.

The mean absolute bioavailability of axitinib after an oral 5 mg dose is 58%.

Compared to overnight fasting, administration of INLYTA with a moderate fat meal resulted in 10% lower AUC and a high fat, high-calorie meal resulted in 19% higher AUC. Compared to overnight fasting, administration of INLYTA with or without food resulted in 10% lower AUC and a high fat, high-calorie meal resulted in 19% higher AUC.

INLYTA can be administered with or without food.

12.4 Drug-Drug Interactions

Effects of Other Drugs on INLYTA: 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, approximately 41% of the radioactivity was recovered in feces and approximately 23% 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 ≤40-fold less in vitro potency against VEGFR-2 compared to axitinib.

INLYTA can be administered with or without food. In vitro studies demonstrated that axitinib has the potential to inhibit CYP1A2 and CYP2C8. However, co-administration of axitinib with paxilactax, a CYP2C8 substrate, did not increase plasma concentrations of paxilactax in patients.

In vitro studies indicated that axitinib does not inhibit CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations. In vitro studies in human hepatocytes indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5.

Axitinib is an inhibitor of the efflux transporter P-glycoprotein (P-gp) in vitro. However, INLYTA is not expected to inhibit P-gp at therapeutic plasma concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with axitinib.

Axitinib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and was not clastogenic in the in vitro human lymphocyte chromosome aberration assay. Axitinib was genotoxic in the in vivo mouse bone marrow micronucleus assay.

INLYTA has the potential to impair reproductive function and fertility in humans. In repeat-dose toxicology studies, findings in the male reproductive tract were observed in the testes/epididymis (decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hyposperma or abnormal sperm forms, reduced sperm density and count) at ≤15 mg/kg/dose administered orally twice daily in mice (approximately 7 times the systemic exposure (AUC) in patients at the recommended starting dose) and ≥15 mg/kg/dose administered orally twice daily in dogs (approximately 0.1 times the AUC in patients at the recommended starting dose). 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 ≤5 mg/kg/dose (approximately 1.5 or 0.3 times the AUC in patients at the recommended starting dose compared to mice and dogs, respectively).

In a fertility study in mice, axitinib did not affect mating or fertility rate when administered orally twice daily to males at any dose tested up to 50 mg/kg/dose following at least 70 days of treatment with axitinib (approximately 57 times the AUC in patients at the recommended starting dose). In female mice, reduced fertility and embryonic viability were observed at all doses tested (≥15 mg/kg/dose administered orally twice daily) following at least 15 days of treatment with axitinib (approximately 10 times the AUC in patients at the recommended starting dose).

14 CLINICAL STUDIES

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). Progression-free survival (PFS) was assessed by a blinded independent central review committee. Other 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-alpha), 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 (median 61 years), gender (72% male), race (75% white, 21% Asian), Eastern Cooperative Oncology Group (ECOG) performance status (55% 0, 45% 1), and histology (96% clear cell).

There was a statistically significant advantage for INLYTA over sorafenib for the endpoint of PFS (see Table 3 and Figure 2). There was no statistically significant difference between the arms in OS.

Table 3. Efficacy Results

<table>
<thead>
<tr>
<th>Endpoint/Study Population</th>
<th>INLYTA</th>
<th>Sorafenib</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ITT</td>
<td>N = 361</td>
<td>N = 362</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (^\text{a}) in months (95% CI)</td>
<td>6.7 (6.3, 8.6)</td>
<td>4.7 (4.6, 5.6)</td>
<td>0.67 (0.54, 0.81)</td>
<td>&lt;0.0001 (^\text{b})</td>
</tr>
<tr>
<td>Median OS in months (95% CI)</td>
<td>20.1 (16.7, 23.4)</td>
<td>19.2 (17.5, 22.3)</td>
<td>0.97 (0.80, 1.17)</td>
<td>NS</td>
</tr>
<tr>
<td>ORR (^\text{a}%) (95% CI)</td>
<td>19.4 (15.4, 23.9)</td>
<td>9.6 (6.6, 12.9)</td>
<td>2.06 (1.41, 3.00)</td>
<td></td>
</tr>
</tbody>
</table>

PFS by prior treatment

Sunitinib-refractory subgroup

| Median, months (95% CI) | 4.8 (4.5, 6.4) | 3.4 (2.8, 4.7) | 0.74 (0.57, 0.96) |         |

Cytokine-refractory subgroup

| Median, months (95% CI) | 12.1 (10.1, 13.9) | 6.5 (6.3, 8.3) | 0.46 (0.32, 0.68) |         |

CI: Confidence interval; HR: Hazard ratio (INLYTA/sorafenib); ITT: Intent to treat; ORR: Objective response rate; NS: Not significant; OS: Overall survival; PFS: Progression-free survival

\(^\text{a}\) Time from randomization to progression or death due to any cause, whichever occurs first.

\(^\text{b}\) Assessed by independent radiology review according to RECIST.

\(^\text{c}\) One-sided p-value from a log-rank test of treatment stratified by EOCG performance status and prior therapy (comparison is considered statistically significant if the one-sided p-value is <0.023).

\(^\text{d}\) 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.

\(^\text{e}\) P-value not included since it was not adjusted for multiple testing.

Figure 2. Kaplan-Meier Curve for Progression Free Survival by Independent Assessment (Intent-to-Treat Population)

17.1 Hypertension

Advise patients that hypertension may develop during INLYTA treatment and that blood pressure should be monitored regularly during treatment [see Warnings and Precautions (5.1)].

17.2 Arterial/Venous Thromboembolic Events

Advise patients that arterial and venous thromboembolic events have been observed during INLYTA treatment, and to inform their doctor if they experience symptoms suggestive of thromboembolic events [see Warnings and Precautions (5.2, 5.3)].

17.3 Hemorrhage

Advise patients that INLYTA may increase the risk of bleeding and to promptly inform their doctor of any bleeding episodes [see Warnings and Precautions (5.4)].

17.4 Cardiac Failure

Advise patients that cardiac failure may develop during INLYTA treatment and that signs or symptoms of cardiac failure should be regularly monitored for during treatment [see Warnings and Precautions (5.5)].

17.5 Gastrointestinal Disorders

Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during INLYTA treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking INLYTA [see Warnings and Precautions (5.6) and Adverse Reactions (6.1)].

17.6 Abnormal Thyroid Function

Advise patients that abnormal thyroid function may develop during INLYTA treatment and to inform their doctor if symptoms of abnormal thyroid function occur [see Warnings and Precautions (5.7)].

17.7 Wound Healing Complications

Advise patients to inform their doctor if they have an unhealed wound or if they have surgery scheduled [see Warnings and Precautions (5.8)].

17.8 Reversible Posterior Leukoencephalopathy Syndrome

Advise patients to inform their doctor if they have worsening of neurological function consistent with RPLS (headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances) [see Warnings and Precautions (5.9)].

17.9 Pregnancy

Advise patients that INLYTA can cause birth defects or fetal loss and that they should not become pregnant during treatment with INLYTA. Both male and female patients should be counseled to use effective birth control during treatment with INLYTA. Female patients should also be advised against breast-feeding while receiving INLYTA [see Warnings and Precautions (5.13) and Use in Specific Populations (8.3)].

17.10 Concomitant Medications

Advise patients to inform their doctor of all concomitant medications, vitamins, or dietary and herbal supplements.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

PATIENT INFORMATION

INLYTA® (in-ly-ta) (axitinib) tablets

Read this Patient Information before you start taking INLYTA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is INLYTA?

INLYTA is a prescription medicine used to treat advanced kidney cancer (advanced renal cell carcinoma or RCC) when one prior drug treatment for this disease has not worked. It is not known if INLYTA is safe or effective in children.

What should I tell my doctor before taking INLYTA?

Before you take INLYTA, tell your doctor if you:

- have high blood pressure
- have thyroid problems
- have liver problems
- have a history of blood clots in your veins or arteries (types of blood vessels), including stroke, heart attack, or change in vision
- have any bleeding problems
- have a history of heart failure
- have an unhealed wound
- plan to have surgery. You should stop taking INLYTA at least 24 hours before planned surgery.
- have any other medical conditions

For females, tell your doctor if you:

- are pregnant or plan to become pregnant. Taking INLYTA during pregnancy can cause the death of an unborn baby or birth defects. You should not become pregnant while taking INLYTA. Talk to your doctor if you are pregnant or plan to become pregnant.
- are able to become pregnant. You should use effective birth control during your treatment with INLYTA. Talk to your doctor about birth control methods to prevent pregnancy while you are taking INLYTA.
- are breastfeeding or plan to breastfeed. It is not known if INLYTA passes into your breast milk. You and your doctor should decide if you will take INLYTA or breastfeed. You should not do both.

For males:

- use effective birth control during your treatment with INLYTA. Talk to your doctor about birth control methods.
- if your female partner becomes pregnant while you are taking INLYTA, tell your doctor right away.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. INLYTA and certain other medicines can affect each other causing serious side effects. Especially tell your doctor if you take:

- dexamethasone
- bosentan
- modafinil
- St. John’s wort (Hypericum perforatum)
INLYTA may cause serious side effects, including:

- **Tear in your stomach or intestinal wall (perforation).** A tear in your stomach or intestinal wall can be serious and can sometimes lead to death. Get medical help right away if you get the following symptoms:
  - severe stomach (abdominal) pain or stomach pain that does not go away
  - vomit blood
  - red or black stools

- **Increased protein in your urine.** Your doctor may decrease your dose of INLYTA or stop your treatment.

- **Problems thinking.** Your doctor should do blood tests before and during your treatment with INLYTA:
  - blood clots which can be serious, and sometimes lead to death. Get emergency help and call your doctor if you get:
    - cough up blood or blood clots
    - bruises that happen without a known cause or get larger
    - red or black stools (looks like tar)
    - pink or brown urine
    - menstrual bleeding or vaginal bleeding that is heavier than normal
    - unusual bleeding from the gums
    - bruising that happens with a known cause or gets larger
    - blood or blood clots
    - vomit blood or vomit looks like “coffee grounds”
  - high blood pressure
  - problems thinking

- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** A condition called reversible posterior leukoencephalopathy syndrome (RPLS) can happen while taking INLYTA. Call your doctor right away if you get:
  - headache
  - seizures
  - weakness
  - confusion
  - high blood pressure
  - blindness or change in vision

- **HIV or AIDS
- tuberculosis
- asthma
- cancer
- depression
- fungal infections
- bacterial infections
- seizures
- headaches, feeling dizzy or weak
- unexpected pain, swelling, or joint pain
- constipation

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of INLYTA. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store INLYTA?**

- Store INLYTA at room temperature between 68°F to 77°F (20°C to 25°C).

- Keep INLYTA and all medicines out of the reach of children.

**General information about INLYTA.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use INLYTA for a condition for which it was not prescribed. Do not give INLYTA to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about INLYTA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about INLYTA that is written for health professionals. For more information, go to www.inlyta.com or call 877-744-5675.

**What are the ingredients in INLYTA?**

**Active ingredient:** axitinib

**Inactive ingredients:** microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry® II red 32K15441. The Opadry II red 32K15441 film coating contains: lactose monohydrate, HPMC 2910/Hypromellose 15cP, titanium dioxide, triacetin (glycerol triacetate), and red iron oxide.