PRODUCT MONOGRAPH

PrINLYTA®

Axitinib

Tablets, 1 mg, 3 mg, 5 mg and 7 mg

Kinase Inhibitor, Anti-Tumour Agent

©Pfizer Products ULC
17,300 Trans-Canada Highway
Kirkland, Quebec
H9J 2M5

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§not commercially available in Canada
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Tablet 1 mg, 3 mg, 5 mg, 7 mg</td>
<td>Lactose monohydrate For a complete listing see Dosage Forms, Composition and Packaging section.</td>
</tr>
</tbody>
</table>

INDICATIONS AND CLINICAL USE

INLYTA (axitinib) is indicated for the treatment of patients with metastatic renal cell carcinoma (RCC) of clear cell histology after failure of prior systemic therapy with either a cytokine or the VEGFR-TKI, sunitinib.

The clinical effectiveness of INLYTA is based on progression-free survival (PFS) in patients with metastatic RCC in a Phase 3, controlled clinical trial which compared INLYTA to sorafenib. The overall median PFS increased by 2 months in patients treated with INLYTA as compared to those treated with sorafenib (HR = 0.67 [95% CI: 0.54, 0.81]). The difference in median PFS for patients previously treated with a cytokine was 5.6 months (HR = 0.46 [95% CI: 0.32, 0.68]), whereas the difference in patients previously treated with sunitinib was 1.4 months (HR = 0.74 [95% CI: 0.57, 0.96]). The overall survival and quality of life were not significantly different in patients treated with INLYTA as compared to those treated with sorafenib (see CLINICAL TRIALS).

INLYTA should be prescribed by a qualified healthcare professional who is experienced in the use of anti-neoplastic therapy.

Geriatrics (≥65 years of age):

In a pivotal, Phase 3 controlled study with INLYTA for the treatment of metastatic RCC, 123/359 (34%) patients treated with INLYTA were ≥ 65 years old. 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 old and patients younger than 65 years. No dosage adjustment is required in patients who are 65 years or older (see
WARNING AND PRECAUTIONS, Special Populations and DOSAGE AND ADMINISTRATION).

**Pediatrics (<18 years of age):**

The safety and efficacy of INLYTA in pediatric patients have not been established. Physeal dysplasia in immature mice and dogs and odontopathies in growing incisors of mice have been observed in toxicology studies. Other toxicities of potential concern to pediatric patients due to the anti-angiogenic mechanism of action of axitinib have not been evaluated in juvenile animals. Therefore, INLYTA should not be administered to children under 18. (see WARNING AND PRECAUTIONS, Special Populations and Conditions and TOXICOLOGY).

**CONTRAINDICATIONS**

INLYTA (axitinib tablets) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

**WARNINGS AND PRECAUTIONS**

<table>
<thead>
<tr>
<th><strong>Serious Warnings and Precautions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>INLYTA should be prescribed by a qualified healthcare professional who is experienced in the use of anti-neoplastic therapy.</td>
</tr>
<tr>
<td>INLYTA has not been studied in patients with severe hepatic impairment (see Hepatic section below)</td>
</tr>
</tbody>
</table>

The following are clinically significant adverse events:

- Hypertension and Hypertensive Crisis (see Cardiovascular section below)
- Arterial Thromboembolism, including deaths (see Cardiovascular section below)
- Venous Thromboembolism, including deaths (see Cardiovascular section below)
- Hemorrhage (including gastrointestinal, cerebral and respiratory tract) (see Hematologic section below)
- Gastrointestinal perforation, including death and gastrointestinal fistulas (see Gastrointestinal section below)
- Reversible posterior leukoencephalopathy syndrome (see Neurologic section below)
- Congestive heart failure/Cardiomyopathy, including deaths (see Cardiovascular section below)
General

INLYTA contains lactose and should not be taken by patients with hereditary problems of lactose intolerance.

Drug-Drug Interactions

Co-administration of INLYTA with strong inhibitors of CYP3A4/5 is not recommended as this may increase axitinib concentrations and drug toxicity. If a strong CYP3A4/5 inhibitor must be co-administered a dose reduction of INLYTA is recommended (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

Co-administration with strong inducers of CYP3A4/5 should be avoided due to the risk of reduced effectiveness of the drug. Moderate CYP3A4/5 inducers may also reduce the plasma exposure of axitinib and should be avoided if possible (see DRUG INTERACTIONS).

Effects on ability to drive and use machines

No studies on the effect of INLYTA on the ability to drive or use machines have been performed. However, patients should be informed that dizziness and fatigue have been reported during treatment with INLYTA.

Carcinogenesis and Mutagenesis

Carcinogenicity studies with axitinib have not been conducted. Axitinib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and was not clastogenic in an in vitro human lymphocyte chromosome aberration assay. Axitinib was genotoxic in an in vivo mouse bone marrow micronucleus test (see TOXICOLOGY).

Cardiovascular

Patients with uncontrolled hypertension at baseline or a recent history of myocardial infarction, uncontrolled angina, coronary/ peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, deep vein thrombosis or pulmonary embolism were excluded from clinical studies with INLYTA.

Hypertension and Hypertensive Crisis

Hypertension is a common adverse event in patients treated with INLYTA (see ADVERSE REACTIONS) and blood pressure should be well controlled prior to initiating treatment with INLYTA. Patients were required to have diastolic BP ≤90 mm Hg and systolic BP ≤140 mm Hg for entry into the controlled Phase 3 trial. During therapy patients should be monitored for hypertension early after starting treatment (no longer than one week after starting axitinib and frequently thereafter to ensure blood pressure control), and treated promptly with a combination of standard anti-hypertensive therapy and INLYTA dose reduction or interruption as clinically warranted. INLYTA should be discontinued if hypertension is severe and persistent despite anti-
hypertensive therapy or if there is evidence of hypertensive crisis (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

In pooled clinical studies for the treatment of patients with RCC, hypertension was reported in 344/672 patients (51%) receiving INLYTA with 155/672 patients (23%) experiencing Grade 3/4 events.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, hypertension was reported in 145/359 patients (40%) receiving INLYTA and 103/355 patients (29%) receiving sorafenib. Grade 3/4 hypertension was observed in 56/359 patients (16%) receiving INLYTA and 39/355 patients (11%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) treated with INLYTA and none in patients treated with 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 treatment and increases in blood pressure were observed as early as 4 days after the first dose of 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 receiving sorafenib (see ADVERSE REACTIONS).

Patients with hypertension that is not controlled by medications should not be treated with INLYTA. If INLYTA is interrupted, patients receiving antihypertensive medications should be monitored for hypotension (see DOSAGE and ADMINISTRATION).

Serious cases of artery dissection have been reported in patients using VEGFR TKIs, including Inlyta, with or without hypertension.

**Congestive Heart Failure/Cardiomyopathy Events**

Congestive heart failure/cardiomyopathy events have been reported in patients receiving INLYTA in the post-market setting. Many events have resulted in hospitalizations and some have been fatal. In clinical studies for the treatment of patients with RCC, congestive heart failure/cardiomyopathy 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 (2%) receiving INLYTA and 11 patients were hospitalized. Grade 3/4 congestive heart failure/cardiomyopathy events were reported in 7 patients (1%) and 2 patients (<1%) receiving INLYTA had fatal events.

In a pivotal controlled Phase 3 clinical study with INLYTA for the treatment of patients with RCC, congestive heart failure/cardiomyopathy events (including cardiac failure, cardiopulmonary failure, left ventricular dysfunction, and right ventricular failure) were reported in 6/359 patients (2%) receiving INLYTA and 3/355 patients (<1%) receiving sorafenib. Grade 3/4 congestive heart failure/cardiomyopathy events were observed in 2 patients (<1%) receiving INLYTA and 1 patient (<1%) receiving sorafenib. Fatal events were reported in 2 patients (<1%) receiving INLYTA and 1 patient (<1%) receiving sorafenib (see ADVERSE REACTIONS).
Monitor for signs or symptoms of congestive heart failure/cardiomyopathy events at baseline and periodically throughout treatment with INLYTA. Management of these events may require temporary interruption or permanent discontinuation and/or dose reduction of INLYTA therapy.

**QT Prolongation**

The effect of INLYTA on the QTc interval was investigated in a randomized, 2-way crossover study where, 35 healthy subjects were administered a single, oral 5 mg dose of INLYTA alone or with 400 mg ketoconazole. Although some tyrosine kinase inhibitors are associated with QT interval prolongation, INLYTA did not result in large mean changes in the QTc interval (>20 msec) up to 3 hours post-dose. However smaller increases in the QTc interval (<10 msec) cannot be ruled out.

**Decreased Heart Rate**

In clinical studies with INLYTA, events of decreased heart rate have occurred (see ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Caution should be observed in patients who are bradycardic or considered to be at risk for bradyarrhythmias or who are receiving other heart rate-lowering drugs.

**Arterial Thromboembolic Events**

In pooled clinical studies for the treatment of patients with RCC, arterial thromboembolic events were reported in 19/672 patients (3%) receiving INLYTA with 17/672 patients (3%) experiencing Grade 3/4 events. Fatal arterial thromboembolic events were reported in 2 patients (<1%) receiving INLYTA.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving INLYTA and 4/355 patients (1%) receiving sorafenib. A fatal cerebrovascular accident was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients (0%) receiving sorafenib (see ADVERSE REACTIONS).

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 clinical studies with INLYTA, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. In pooled clinical studies for the treatment of patients with RCC, venous thromboembolic events were reported in 19/672 patients (3%) receiving INLYTA with 14/672 patients (2%) experiencing Grade 3/4 events. Fatal venous thromboembolic events were reported in 1/672 patients (<1%) receiving INLYTA.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic 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 (including pulmonary embolism, deep vein thrombosis, and retinal-vein occlusion/thrombosis) were reported in 9/359 patients (3%) receiving INLYTA and 2/355 patients (1%) receiving sorafenib.

INLYTA should be used with caution in patients who are at risk for venous thromboembolic events 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.

**Endocrine and Metabolism**

**Thyroid Dysfunction**

In clinical studies with INLYTA, events of hypothyroidism and hyperthyroidism have occurred (see ADVERSE REACTIONS). In pooled clinical studies for the treatment of patients with RCC, hypothyroidism was reported in 165/672 patients (25%) receiving INLYTA. In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, hypothyroidism was reported in 69/359 patients (19%) receiving INLYTA and 29/355 patients (8%) receiving sorafenib.

In pooled clinical studies for the treatment of patients with RCC, hyperthyroidism was reported in 11/672 patients (2%) receiving INLYTA. In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, 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 (see ADVERSE REACTIONS).

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

**Gastrointestinal**

**Gastrointestinal Perforation and Fistula Formation**

In clinical studies with INLYTA, events of gastrointestinal (GI) perforation or fistula have occurred, including a fatal GI perforation (see ADVERSE REACTIONS). In pooled clinical studies for the treatment of patients with RCC, gastrointestinal perforation and fistula were reported in 13/672 patients (2%) receiving INLYTA. In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical studies with INLYTA, GI perforation was reported in 5/715 patients (1%), including one death, and GI fistulas were reported in 4/715 patients (1%).

Monitoring for symptoms of GI perforation or fistula formation periodically throughout treatment with INLYTA is recommended.
**Hematologic**

**Elevation of Hemoglobin or Hematocrit**

In clinical studies with INLYTA, events of elevated hemoglobin have occurred. Elevated hemoglobin above the upper limit of normal (ULN) was observed in 31/320 patients (10%) receiving INLYTA and 3/316 patients (1%) receiving sorafenib. An increase in red blood cell mass may increase the risk of thromboembolic events.

Monitoring hemoglobin or hematocrit before initiation of, and periodically throughout, treatment with INLYTA is recommended. 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.

**Hemorrhagic**

In clinical studies with INLYTA, hemorrhagic events have been reported, some of which were fatal (see ADVERSE REACTIONS). In pooled clinical studies for the treatment of patients with RCC, hemorrhagic events were reported in 173/672 patients (26%) receiving INLYTA with 27/672 patients (3%) experiencing Grade 3/4 events. Fatal hemorrhagic events were reported in 3/672 patients (<1%) receiving INLYTA.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic 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 patients (1%) receiving INLYTA (including cerebral hemorrhage, hematuria, hemoptyisis, 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.

Since INLYTA has not been studied in patients who have evidence of untreated brain metastasis, a history of pulmonary embolism in the previous 6 months, or a history of active bleeding in the previous 3 months, treatment with INLYTA is not recommended in these patients. INLYTA should be used with caution in patients with a significant risk for hemorrhage.

**Hepatic**

**Elevation of Liver Enzymes**

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, alanine aminotransferase (ALT) elevations occurred in 74/331 patients (22%) receiving INLYTA and 68/313 patients (22%) receiving sorafenib. Grade 3/4 events were reported in 1/331 patients (<1%) receiving INLYTA and 5/313 patients (2%) receiving sorafenib (see ADVERSE REACTIONS).

Monitoring of ALT, aspartate aminotransferase (AST) and bilirubin before initiation of, and periodically throughout treatment with, INLYTA is recommended.
Hepatic Impairment

In a clinical hepatic impairment study with INLYTA (N=24 subjects), the systemic exposure of INLYTA was approximately 2-fold higher in patients with moderate hepatic impairment (Child-Pugh class B) compared to patients 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 patient population (see DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY).

Neurologic

Reversible Posterior Leukoencephalopathy Syndrome

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

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, RPLS was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. Two additional events of RPLS were reported in other clinical trials with INLYTA (see ADVERSE REACTIONS).

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. INLYTA should be discontinued in patients with signs/symptoms of RPLS. The safety of reinitiating INLYTA therapy in patients previously experiencing RPLS is not known.

Peri-Operative Considerations

Wound Healing Complications

No formal studies of the effect of INLYTA on wound healing have been conducted. Since vascular endothelial growth factor (VEGF) inhibitors may impair wound healing, treatment with INLYTA should be stopped at least 24 hours prior to scheduled surgery. The decision to resume INLYTA after surgery should be based on clinical judgement of adequate wound healing. INLYTA should be discontinued in patients with wound dehiscence.

Renal

Renal Impairment

Axitinib has not been studied in patients with renal impairment. Caution should be exercised when administering INLYTA to patients with end-stage renal disease. Population pharmacokinetic analyses, suggest that there is no significant change in axitinib clearance in
patients with mild to severe renal impairment. No dose adjustments based on renal function are required in patients with mild to severe renal impairment (see DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY).

Proteinuria

In pooled clinical studies for the treatment of patients with RCC, proteinuria was reported in 142/672 patients (21%) receiving INLYTA with 33/672 patients (5%) experiencing Grade 3/4 events.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic 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 (see ADVERSE REACTIONS).

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with INLYTA is recommended. For patients who develop moderate to severe proteinuria, reduction of the dose or temporary interruption of INLYTA treatment is recommended.

Sexual Function/Reproduction

Based on nonclinical safety findings, male and female fertility may be impaired by treatment with axitinib (see TOXICOLOGY).

Skin and Subcutaneous Tissue Disorders

Palmar-Plantar Erythrodysesthesia Syndrome

In pooled clinical studies for the treatment of patients with RCC, palmar-plantar erythrodysesthesia syndrome (PPE) was reported in 216/672 patients (32%) receiving INLYTA with 51/672 patients (7.6%) experiencing Grade 3/4 events.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, PPE was reported in 98/359 patients (27%) receiving INLYTA and 181/355 patients (51%) receiving sorafenib (see ADVERSE REACTIONS). Grade 3 PPE was reported in 18/359 (5%) of patients in the INLYTA arm and 57/355 (16.1%) of patients in the sorafenib arm. PPE resulted in dose modification or temporary delay of treatment in 19/359 (5.3%) patients treated with INLYTA and 63/355 (17.7%) patients treated with sorafenib. PPE led to treatment discontinuation in 1/359 (0.3%) of patients treated with INLYTA and 4/355 (1.1%) of patients treated with sorafenib.

Consider initiating treatment with topical therapies as soon as symptoms occur.
**Special Populations**

**Pregnant Women**

INLYTA should not be used during pregnancy. There are no studies in pregnant women using INLYTA. Based on its anti-angiogenic mechanism of action, INLYTA is expected to cause fetal harm when used by pregnant women.

In developmental toxicity studies in mice, axitinib was teratogenic, embryotoxic and fetotoxic at maternal exposures that were lower than human exposures at the recommended clinical dose (see TOXICOLOGY).

Women of childbearing potential should be advised to avoid becoming pregnant while receiving INLYTA. It is recommended that men and women should use effective birth control during treatment with INLYTA.

**Nursing Women**

The safe use of axitinib during lactation has not been established. It is unknown whether INLYTA is excreted in human milk. Breastfeeding should be discontinued during treatment with INLYTA.

Many drugs are commonly excreted in human milk therefore INLYTA may be toxic to nursing infants.

**Pediatrics (<18 years of age)**

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

Limited data are available on the use of INLYTA in pediatric patients. In a phase 1 dose-finding study, the safety of INLYTA was evaluated in 16 pediatric patients with recurrent/refractory solid tumours. The maximum tolerated dose was determined to be 2.4 mg/m²/dose administered orally twice daily in 28-day cycles. There were three Grade 3 non-dose limiting toxicities (DLTs) reported: hemoglobin increased, hypertension, and lipase increased. DLTs (palmar-plantar erythrodysesthesia syndrome and intratumoural hemorrhage) occurred in 2/5 patients treated at 3.2 mg/m²/dose.

Physeal dysplasia in immature mice and dogs and odontopathies in growing incisors of mice have been observed in toxicology studies. Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals (see TOXICOLOGY). Therefore, INLYTA should not be administered to children less than 18 years of age.

**Geriatrics (≥65 years of age)**

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, 123/359 (34%) of patients 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 old and patients younger than 65 years. No dosage adjustment is required in patients who are 65 years or older (see DOSAGE AND ADMINISTRATION).

**Monitoring and Laboratory Tests**

Prior to treatment and during the course of therapy with INLYTA, patients should be monitored for hypertension, signs or symptoms of congestive heart failure/cardiomyopathy events, decreased heart rate, thyroid dysfunction, increased hemoglobin or hematocrit, symptoms of gastrointestinal perforation and fistula formation, proteinuria and elevated liver enzymes and elevated creatinine (see WARNINGS and PRECAUTIONS, Hypertension, Thyroid Dysfunction, Elevation of Hemoglobin and Hematocrit, Gastrointestinal Perforation and Fistula Formation, Proteinuria, Elevation of Liver Enzymes).

**ADVERSE REACTIONS**

**Adverse Drug Reaction Overview**

The safety of INLYTA has been evaluated in 672 patients with metastatic RCC. The data described in this section reflect exposure to INLYTA in 359 patients with metastatic RCC who participated in the pivotal Phase 3 controlled clinical study versus sorafenib (see CLINICAL TRIALS).

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 event occurred in 199/359 patients (55%) receiving INLYTA and 220/355 patients (62%) receiving sorafenib. Permanent discontinuation due to an adverse event occurred in 33/359 patients (9%) receiving INLYTA and 46/355 patients (13%) receiving sorafenib.

**Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Potentially serious adverse reactions with INLYTA included congestive heart failure/cardiomyopathy events, hypertension and hypertensive crisis, arterial thrombotic events, venous thrombotic events, cardiac dysfunction, hemorrhagic events, gastrointestinal perforation and fistula formation, thyroid dysfunction, elevation of hemoglobin or hematocrit, wound healing complications, RPLS, proteinuria, palmar-plantar erythrodysesthesia syndrome, elevation of liver enzymes and fetal development (see WARNINGS AND PRECAUTIONS).
Table 1 presents the most common adverse reactions reported in ≥10% of patients who received INLYTA or sorafenib.

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

<table>
<thead>
<tr>
<th>Adverse Reactiona</th>
<th>INLYTA (N=359)</th>
<th>Sorafenib (N=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Gradesb</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>Asthenia</td>
<td>21c</td>
<td>5</td>
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<tr>
<td>Mucosal inflammation</td>
<td>15</td>
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<tr>
<td>Investigations</td>
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<td></td>
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<td>Weight decreased</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
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</tr>
<tr>
<td>Decreased appetite</td>
<td>34c</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
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<tr>
<td>Arthralgia</td>
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<tr>
<td>Pain in extremity</td>
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<td>Nervous system disorders</td>
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<td>Renal and urinary disorders</td>
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<td>Proteinuria</td>
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<td>Respiratory, Thoracic and Mediastinal disorders</td>
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<td>Dysphonia</td>
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<td>Cough</td>
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</tr>
<tr>
<td>Dyspnea</td>
<td>15c</td>
<td>2</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythodysesthesia syndrome</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Rash</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Haemorrhageb</td>
<td>16c</td>
<td>1</td>
</tr>
</tbody>
</table>

*a Percentages are treatment-emergent, all-causality events; b National Cancer Institute Common Terminology Criteria for
Adverse Events, Version 3.0; *Includes Grade 5 <1%; **Hemorrhage includes the following preferred terms (All Grades frequency): epistaxis (6%), haematuria (3%), haemoptysis (2%), rectal haemorrhage (2%), cerebral haemorrhage (<1%), gastric haemorrhage (<1%), and lower gastrointestinal haemorrhage (<1%).

**Less Common Clinical Trial Adverse Drug Reactions (<10%)**

Selected adverse reactions (all grades) that were reported in <10% of patients treated with INLYTA included the following:

**Blood and lymphatic disorders:** anemia (4%), neutropenia (<1%), leukopenia (<1%), polycythemia (1%), thrombocytopenia (2%)

**Cardiac disorder:** congestive heart failure/cardiomyopathy events including cardiac failure (1%), cardiopulmonary failure (<1%), left ventricular dysfunction (<1%), right ventricular failure (<1%)

**Metabolism and nutrition disorders:** dehydration (6%), hypercalcemia (3%), hyperkalemia (3%)

**Nervous system disorders:** dizziness (9%), RPLS (<1%)

**Eye disorders:** retinal artery occlusion (<1%)

**Ear and labyrinth disorders:** tinnitus (3%)

**Endocrine disorders:** hyperthyroidism (1%)

**Vascular disorders:** hypertensive crisis (1%); venous embolic and thrombotic events including pulmonary embolism (2%), retinal-vein occlusion/thrombosis (1%), and deep vein thrombosis (1%); arterial embolic and thrombotic events including transient ischaemic attack (1%), cerebrovascular accident (<1%), and myocardial infarction (<1%)

**Respiratory, thoracic and mediastinal disorders:** epistaxis (6%), hemoptysis (2%), pulmonary embolism (2%)

**Gastrointestinal disorders:** upper abdominal pain (8%), hemorrhoids (4%), fistula (<1%), anal fistula (<1%), gastrointestinal perforation (<1%)

**Musckeletal and connective tissue disorders:** myalgia (7%)

**Renal and urinary disorders:** renal failure (including acute renal failure) (2%)

**Skin and subcutaneous tissue disorders:** glossodynia (3%)

**Investigations:** lipase increased (3%)
Abnormal Hematologic and Clinical Chemistry Findings

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>INLYTA</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>All Grades</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>320</td>
<td>35</td>
</tr>
<tr>
<td>Lymphocytes (absolute)</td>
<td>317</td>
<td>33</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>312</td>
<td>15</td>
</tr>
<tr>
<td>White blood cells</td>
<td>320</td>
<td>11</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>336</td>
<td>55</td>
</tr>
<tr>
<td>Bicarbonate decreased</td>
<td>314</td>
<td>44</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>336</td>
<td>39</td>
</tr>
<tr>
<td>ALP increased</td>
<td>336</td>
<td>30</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>336</td>
<td>28</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>338</td>
<td>27</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>338</td>
<td>25</td>
</tr>
<tr>
<td>ALT increased</td>
<td>331</td>
<td>22</td>
</tr>
<tr>
<td>AST increased</td>
<td>331</td>
<td>20</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>338</td>
<td>17</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>337</td>
<td>15</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>333</td>
<td>15</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>336</td>
<td>11</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>338</td>
<td>13</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>336</td>
<td>13</td>
</tr>
</tbody>
</table>

*National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0
ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase

Hemoglobin increases above the upper limit of normal were observed for 9% of patients treated with INLYTA as compared to 1% of patients treated with sorafenib. Neutrophils decreased was observed in 6% of patients treated with INLYTA and 8% of patients treated with sorafenib.

In clinical trials, INLYTA was associated with statistically significant mean increases from baseline in systolic and diastolic blood pressure. On day 15 of treatment, systolic blood pressure was increased by mean 8.0 mmHg and diastolic blood pressure by mean 5.5 mmHg. These blood pressure increases were associated with a statistically significant mean decrease from baseline in heart rate of approximately 4 to 6 beats per minute.
Hypercalcemia was observed in 6% of patients treated with INLYTA and 2% of patients treated with sorafenib.

Hyperbilirubinemia was observed in 1% of patients treated with INLYTA and 1% of patients treated with sorafenib.

Post-Marketing Experience

The following adverse reactions have been identified during post approval use of INLYTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorder: Acute pulmonary oedema, cardiac failure, cardiac failure congestive, cardiomyopathy, cardiopulmonary failure, central venous pressure increased, diastolic dysfunction, ejection fraction decreased, left ventricular dysfunction, left ventricular failure, stress cardiomyopathy, pulmonary oedema, and ventricular dysfunction

Vascular disorders: Artery dissection and artery aneurysm (including rupture) have been reported in association with VEGFR TKIs, including Inlyta.

DRUG INTERACTIONS

Overview

Axitinib is metabolized in the liver, undergoing oxidative metabolism mediated primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, as well as uridine diphosphate-glucuronosyltransferase (UGT) 1A1. The aqueous solubility of axitinib is pH dependent, with higher pH resulting in lower solubility.

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 does not induce CYP1A1, CYP1A2, or CYP3A4/5.

In vitro studies indicated that axitinib has a potential to inhibit CYP1A2 and CYP2C8. Co-administration of INLYTA with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g., theophylline).

In vitro studies indicated that axitinib inhibits P-glycoprotein. However, INLYTA is not expected to inhibit P-glycoprotein at therapeutic plasma concentrations.

Drug-Drug Interactions

CYP3A4/5 Inhibitors
Co-administration of INLYTA with strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) should be avoided as they may increase the plasma concentration of axitinib. 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 reduction of INLYTA is recommended (see DOSAGE AND ADMINISTRATION).

Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean AUC 2-fold and $C_{\text{max}}$ 1.5-fold of a single 5-mg oral dose of INLYTA in healthy volunteers.

**CYP3A4/5 Inducers**

Co-administration of INLYTA with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, and phenobarbital) should be avoided due to the potential for reduced effectiveness of the drug. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma concentration of axitinib and should be avoided if possible. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended (see DOSAGE AND ADMINISTRATION).

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 $C_{\text{max}}$ by 71% of a single 5-mg dose of INLYTA in healthy volunteers.

**Agents that Increase Gastric pH**

The solubility of axitinib is lowered with increasing pH and co-administration of drugs that increase the gastric pH (e.g. proton pump inhibitors, H2-receptor antagonists, and antacids) could result in decreased plasma exposure to axitinib. It is recommended that antacids should be avoided for 2 hours before through 2 hours after dosing with INLYTA.

The effect of rabeprazole, a proton pump inhibitor (administered 20 mg once a day), on the steady state exposure of axitinib (dosed at 5 mg twice a day) was examined in 6 patients with solid tumors. Although the mean AUC and $C_{\text{max}}$ of axitinib were decreased by 15% (geometric mean ratio of 0.85 [90% CI: 0.59, 1.23]) and 42% (geometric mean ratio of 0.58 [90% CI: 0.26, 1.30]), respectively, in the presence of rabeprazole, the magnitude of the effect of the proton pump inhibitor was variable between patients.

**Drug-Food Interactions**

Grapefruit, grapefruit juice, and products containing grapefruit extract may increase axitinib plasma concentrations and should be avoided.

INLYTA may be administered with or without food (see DOSAGE AND ADMINISTRATION). 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 (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

**Drug-Herb Interactions**

Interactions with herbal products have not been established. St. John’s wort (*Hypericum perforatum*), is an inducer of CYP3A4/5, that may decrease axitinib plasma concentrations and should be avoided.

**Drug-Laboratory Interactions**

Interactions between INLYTA and laboratory tests have not been studied.

**DOSAGE AND ADMINISTRATION**

**Recommended Dose and Dosage Adjustment**

The recommended oral starting dose of INLYTA is 5 mg twice daily (see CLINICAL TRIALS). INLYTA may be taken with or without food (see ACTION AND CLINICAL PHARMACOLOGY). INLYTA should be swallowed whole with a glass of water.

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 Common Toxicity Adverse Event Criteria [CTCAE]) for two consecutive weeks, are normotensive, and are not receiving anti-hypertension 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 (see WARNINGS AND PRECAUTIONS). When dose reduction is necessary, the INLYTA dose may be reduced from 5 mg twice daily to 3 mg twice daily and further to 2 mg twice daily.

**Geriatric**

No alteration of dosage, dosing frequency or route of administration is required in patients over 65 years.

**Pediatric**

Health Canada has not authorized an indication for pediatric use (see INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS, Special Populations).

**Hepatic Impairment**
No dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). Based on pharmacokinetic data, the starting dose of INLYTA should be decreased by approximately half in 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 patient population as an appropriate starting dose is unknown (see WARNINGS AND PRECAUTIONS, Hepatic Impairment, ACTION AND CLINICAL PHARMACOLOGY).

Renal Impairment

Axitinib has not been studied in patients with renal impairment. Caution should be exercised when administering INLYTA to patients with end-stage renal disease. No dose adjustments based on renal function are required in patients with mild to severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY).

Strong CYP3A4/5 Inhibitors

Co-administration of INLYTA with strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations and is not recommended (see DRUG INTERACTIONS).

Missed Dose

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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is no specific treatment for INLYTA overdose.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic 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.
ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Axitinib was shown to inhibit tyrosine kinase VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumor growth, and metastatic progression of cancer. In vitro, axitinib has been shown to inhibit VEGF-mediated endothelial cell proliferation and survival. In vivo, axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumor vasculature that expressed the target in vivo and produced tumor growth delay, regression, and inhibited metastases in many experimental models of cancer.

Pharmacodynamics

Electrocardiography

In a randomized, 2-way crossover study, 35 healthy subjects were administered a single oral 5 mg dose of INLYTA alone or on day 4 of a 7 day treatment with 400 mg/day ketoconazole. Axitinib at 5 mg was associated with a mean decrease in heart rate of 5 beats per minute. INLYTA did not result in large mean changes in the QTc interval (> 20 msec) up to 3 hours post-dose, however smaller increases in the QTc interval (< 10 msec) cannot be ruled out.

Pharmacokinetics

Table 3. Axitinib Pharmacokinetic Parameter in Patients with Metastatic Renal Cell Carcinoma after Administration of 5 mg Axitinib Twice Daily for 15 Days (N=20)

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h/mL)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt; (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean (% CV)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27.8 (79)</td>
<td>265 (77)</td>
<td>2.00 (1.0-2.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup>% CV is the coefficient of variation around the arithmetic mean.

<sup>b</sup>T<sub>max</sub> reported as median and range.

Absorption

Following administration of a single, oral 5 mg dose of axitinib, the median time to achieve peak concentrations ranged from 2.5 to 4.1 hours. Daily dosing results in approximately 1.4-fold accumulation as compared to administration of a single dose. Axitinib exhibits approximately linear steady-state pharmacokinetics at doses between 1 mg and 20 mg. The mean absolute bioavailability of axitinib following administration of a single, oral 5 mg dose of axitinib is 58%.

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.
**Distribution**

Axitinib is highly bound (>99%) to human plasma proteins with preferential binding to albumin and moderate binding to α1-acid glycoprotein. In patients with metastatic RCC (n=20), at the 5 mg twice daily dose in the fed state, the geometric mean (CV%) for clearance and apparent volume of distribution were 38 (80%) L/h and 160 (105%) L, respectively.

**Metabolism**

Axitinib is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

**Excretion**

The plasma half-life of axitinib ranges from 2.5 to 6.1 hours with steady state expected within 2 to 3 days of dosing.

Following oral administration of a 5-mg radioactive dose of axitinib, approximately 41% of the radioactivity was recovered in feces and 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 represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity. The sulfoxide and N-glucuronide metabolites show approximately 400-fold and 8000-fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

**Special Populations and Conditions**

**Age, Gender, and Race:** Population pharmacokinetic analyses from patients with metastatic cancer (including metastatic 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.

**Pediatrics (< 18 years):** The safety and efficacy of INLYTA in pediatric patients have not been established. (See INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS, Special Populations and Conditions).

**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 patients with mild hepatic impairment (Child-Pugh class A) and approximately 2-fold higher in 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 DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, Special Populations).
Renal Impairment: INLYTA has not been studied in patients with renal impairment. Population pharmacokinetic analysis (based on pre-existing renal function) was carried out in 590 healthy volunteers and patients, including five with severe renal impairment (15 mL/min ≤ CLcr < 29 mL/min), 64 with moderate renal impairment (30 mL/min ≤ CLcr < 59 mL/min), and 139 with mild renal impairment (60 mL/min ≤ CLcr < 89 mL/min). Mild to severe renal impairment did not have meaningful effects on the pharmacokinetics of axitinib. Data from only one patient with end-stage renal disease are available.

STORAGE AND STABILITY

Store at a controlled room temperature of 25°C; excursions permitted to 15-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

INLYTA tablets are supplied as follows:

- 1 mg: red, film-coated, oval tablets debossed with “Pfizer” on one side and “1 XNB” on the other and containing 1 mg of axitinib
- 3 mg: red film-coated, round tablets, debossed with “Pfizer” on one side and “3 XNB” on the other side and containing 3 mg of axitinib.
- 5 mg: red, film-coated, triangular tablets debossed with “Pfizer” on one side and “5 XNB” on the other and containing 5 mg of axitinib.
- 7 mg: red film-coated, diamond-shaped tablets, debossed with “Pfizer” on one side and “7 XNB” on the other side and containing 7 mg of axitinib.

Both tablets contain the following excipients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry II red as inactive ingredients. The Opadry II red film coating contains lactose monohydrate, HPMC 2910/Hypromellose 15cP, titanium dioxide, triacetin (glycerol triacetate), and red iron oxide.

INLYTA 1 mg tablets are presented as follows:

- bottles of 60
- foil/foil blister packs containing 28 ([14 tabs/blister] x [2 blisters]), or 56 ([14 tabs/blister] x [4 blisters]) tablets.
INLYTA 3 mg tablets are presented as follows:

- bottles of 60
- foil/foil blister packs containing 28 ([14 tabs/blister] x [2 blisters]), or 56 ([14 tabs/blister] x [4 blisters]) tablets.

INLYTA 5 mg tablets are presented as follows:

- bottles of 60
- foil/foil blister packs containing 28 ([14 tabs/blister] x [2 blisters]), or 56 ([14 tabs/blister] x [4 blisters]) tablets.

INLYTA 7 mg tablets are presented as follows:

- bottles of 60
- foil/foil blister packs containing 28 ([14 tabs/blister] x [2 blisters]), or 56 ([14 tabs/blister] x [4 blisters]) tablets.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Axitinib

Chemical name: N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl] benzamide

Molecular formula: \( \text{C}_{22}\text{H}_{18}\text{N}_{4}\text{OS} \)

Molecular mass: 386.47 Daltons

Structural formula:

![Structural formula of Axitinib]

Physicochemical properties: 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 \( \mu \text{g/mL} \). The partition coefficient (n-octanol/water) is 3.5.
CLINICAL TRIALS

The safety and efficacy of INLYTA were evaluated in a randomized, open-label, multicenter Phase 3 study. 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). The primary endpoint, progression-free survival (PFS), was assessed using a blinded independent central review. Secondary endpoints included objective response rate (ORR), overall survival (OS), and quality of life (QoL).

Study demographics and trial design

Table 4 presents the patient demographics in the INLYTA Phase 3 clinical study.

Of the 723 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, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.
Table 4.  Summary of Patient Demographics in Phase 3 Trial of INLYTA (Intent to Treat Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>INLYTA N=361 n (%)</th>
<th>Sorafenib N=362 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>238 (66)</td>
<td>238 (66)</td>
</tr>
<tr>
<td>≥65</td>
<td>123 (34)</td>
<td>124 (34)</td>
</tr>
<tr>
<td>Gender</td>
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<td></td>
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<tr>
<td>Male</td>
<td>265 (73)</td>
<td>258 (71)</td>
</tr>
<tr>
<td>Female</td>
<td>96 (27)</td>
<td>104 (29)</td>
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<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>278 (77)</td>
<td>269 (74)</td>
</tr>
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<td>Asian</td>
<td>77 (21)</td>
<td>81 (22)</td>
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<tr>
<td>Black</td>
<td>1 (&lt;1)</td>
<td>4 (1)</td>
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<tr>
<td>Other</td>
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<td>8 (2)</td>
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<td>ECOG performance status</td>
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<td>ECOG 0</td>
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<td>Geographic region</td>
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<td>North America</td>
<td>88 (24)</td>
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<td>Europe</td>
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<td>170 (47)</td>
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<td>Asia</td>
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<td>Other</td>
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<td>15 (4)</td>
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<td>MSKCC risk group</td>
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<td>Favorable</td>
<td>100 (28)</td>
<td>101 (28)</td>
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<td>Intermediate</td>
<td>134 (37)</td>
<td>130 (36)</td>
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<tr>
<td>Poor</td>
<td>118 (33)</td>
<td>120 (33)</td>
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<tr>
<td>NA</td>
<td>9 (2)</td>
<td>11 (3)</td>
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<tr>
<td>Prior Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib-containing regimen</td>
<td>192 (53)</td>
<td>195 (54)</td>
</tr>
<tr>
<td>Cytokine-containing regimen</td>
<td>126 (35)</td>
<td>125 (35)</td>
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<tr>
<td>Bevacizumab-containing regimen</td>
<td>31 (9)</td>
<td>29 (8)</td>
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<tr>
<td>Temsirolimus-containing regimen</td>
<td>12 (3)</td>
<td>13 (4)</td>
</tr>
</tbody>
</table>

ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan-Kettering Cancer Center

Study results

The average daily dose of INLYTA was approximately 5 mg twice daily. There was a statistically significant advantage for INLYTA over sorafenib for the primary endpoint of PFS (see Table 5 and Figures 1 to 3). The magnitude of the increase in median PFS in the axitinib arm as compared to the sorafenib arm varied in subgroups stratified by prior treatment. The subgroups of patients who failed prior therapy with temsirolimus or bevacizumab were too small for a reliable assessment of efficacy data. There was no statistically significant difference in OS between the two treatment arms.
Table 5. Efficacy Results by Independent Assessment

<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><strong>PFS</strong>&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall ITT</td>
<td>N= 361</td>
<td>N = 362</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, 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&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sunitinib-refractory subgroup</td>
<td>N=194</td>
<td>N=195</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>4.8 (4.5, 6.4)</td>
<td>3.4 (2.8, 4.7)</td>
<td>0.74 (0.57, 0.96)</td>
<td>0.0215&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cytokine-refractory subgroup</td>
<td>N=126</td>
<td>N=125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>12.1 (10.1, 13.9)</td>
<td>6.5 (6.3, 8.3)</td>
<td>0.46 (0.32, 0.68)</td>
<td>&lt;0.0001&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall ITT</td>
<td>N=361</td>
<td>N=362</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, 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>Sunitinib-refractory subgroup</td>
<td>N=194</td>
<td>N=195</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>15.2 (12.8, 18.3)</td>
<td>16.5 (13.7, 19.2)</td>
<td>1.00 (0.78, 1.27)</td>
<td>NS</td>
</tr>
<tr>
<td>Cytokine-refractory subgroup</td>
<td>N=126</td>
<td>N=125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>29.4 (24.5, NE)</td>
<td>27.8 (23.1, 34.5)</td>
<td>0.81 (0.56, 1.19)</td>
<td>NS</td>
</tr>
</tbody>
</table>

CI: Confidence interval; CR: Complete response; HR: Hazard ratio (INLYTA/sorafenib); ITT: Intent to treat; NE: Not estimable; NS: not statistically significant; OS: overall survival; PFS: Progression-free survival; PR: Partial response

<sup>a</sup> Time from randomization to progression or death due to any cause, whichever occurs first.

<sup>b</sup> Assessed by independent radiology review according to RECIST.

<sup>c</sup> Two-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 two-sided p-value is <0.023). One-sided p-value is <0.0001 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).

<sup>d</sup> Two-sided p-value from a log-rank test of treatment stratified by ECOG performance status. One-sided p-values for sunitinib and cytokine-refractory subgroups are p=0.0107 and p<0.0001, respectively, from a log-rank test of treatment stratified by ECOG performance status.

The objective response rate (ORR) was assessed by an independent radiology review according to RECIST criteria. Overall, 19.4% [95% CI: 15.4%, 23.9%] of patients in the axitinib treatment arm and 9.4% [95% CI: 6.6%, 12.9%] of patients in the sorafenib arm achieved a confirmed ORR. The risk ratio (RR) was 2.06 [95% CI: 1.41, 3.00], with a two-sided p-value of 0.0001<sup>*</sup>. In the sunitinib-refractory subgroup, ORR was confirmed in 11.3% [95% CI: 7.2%, 16.7%] of patients in the axitinib arm and in 7.7% [95% CI: 4.4%, 12.4%] of patients in the sorafenib arm (RR of 1.48 [95% CI: 0.79, 2.75], two-sided p-value of 0.2169<sup>**</sup>). In the cytokine-refractory subgroup, the ORR was confirmed in 32.5% [95% CI: 24.5%, 41.5%] of patients in the axitinib arm and in 13.6% [95% CI: 8.1%, 20.9%] of patients in the sorafenib arm (RR of 2.39 [95% CI: 1.43, 3.99], two-sided p-value of 0.0004<sup>***</sup>).

<sup>*</sup>One-sided p-value = 0.0001; <sup>**</sup>One-sided p-value = 0.1085; <sup>***</sup>One-sided p-value = 0.0002.
**Figure 1.** Kaplan-Meier Curve for Progression Free Survival by Independent Assessment for Overall Patient Population

- **INLYTA (N=361)**
  - Median 6.7 months

- **Sorafenib (N=362)**
  - Median 4.7 months

Hazard Ratio = 0.67
95% CI [0.54, 0.81]
P value < 0.0001

**Number of Subjects At Risk**

<table>
<thead>
<tr>
<th></th>
<th>INLYTA</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>361</td>
<td>362</td>
</tr>
<tr>
<td>0 months</td>
<td>361</td>
<td>362</td>
</tr>
<tr>
<td>1 month</td>
<td>256</td>
<td>224</td>
</tr>
<tr>
<td>2 months</td>
<td>202</td>
<td>157</td>
</tr>
<tr>
<td>3 months</td>
<td>145</td>
<td>100</td>
</tr>
<tr>
<td>4 months</td>
<td>96</td>
<td>51</td>
</tr>
<tr>
<td>5 months</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>6 months</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>7 months</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>8 months</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>9 months</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10 months</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Figure 2.** Kaplan-Meier Curve for Progression Free Survival by Independent Assessment for Prior Sunitinib Subgroup

- **INLYTA (N=194)**
  - Median 4.8 months

- **Sorafenib (N=195)**
  - Median 3.4 months

Hazard Ratio = 0.74
95% CI [0.57, 0.96]
P value = 0.0215

**Number of Subjects At Risk**

<table>
<thead>
<tr>
<th></th>
<th>INLYTA</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>194</td>
<td>195</td>
</tr>
<tr>
<td>0 months</td>
<td>194</td>
<td>195</td>
</tr>
<tr>
<td>1 month</td>
<td>132</td>
<td>104</td>
</tr>
<tr>
<td>2 months</td>
<td>97</td>
<td>67</td>
</tr>
<tr>
<td>3 months</td>
<td>60</td>
<td>37</td>
</tr>
<tr>
<td>4 months</td>
<td>34</td>
<td>20</td>
</tr>
<tr>
<td>5 months</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>6 months</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>7 months</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>8 months</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>9 months</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10 months</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
The efficacy of INLYTA was independent of the following demographic and baseline disease characteristics: age, gender, race, geographic region, MSKCC status and ECOG status.

In the pivotal study, the QoL assessments were based on self-reported global scores from protocol-specified questionnaires, EuroQoL EQ-5D and FKSI-15. Analysis compared patients on therapy in both arms. Although the assessments showed no statistically significant difference between treatment with axitinib or sorafenib, INLYTA demonstrated a 17% decrease in risk compared to sorafenib for the pre-specified time to deterioration (TTD) composite endpoint, defined as the time to the first occurrence of death, progression or meaningful deterioration in QoL based on the FKSI-15 questionnaire (HR = 0.83 [95% CI: 0.70, 0.98]; 2-sided p-value = 0.0282).

One-sided p-value = 0.0141.
DETAILED PHARMACOLOGY

Also refer to PART I, ACTION AND CLINICAL PHARMACOLOGY.

Nonclinical Pharmacology

Safety Pharmacology

In safety pharmacology studies, there were no axitinib-related respiratory or cardiovascular effects in mice, rats or dogs following the administration of single oral doses of up to 30 mg/kg in mice and dogs and 500 mg/kg in rats. Hemodynamic changes (decreased blood pressure and temporally-related decreases and increases in heart rate relative to vehicle) were observed in the mouse at 30 mg/kg/day following repeat-dose administration (approximately 35 times the human clinical exposure based on AUC at the recommended human starting dose).

In a human ether-à-go-go-related gene (hERG) potassium channel assay, 7% inhibition was observed at 3 µM, the highest evaluable concentration. The IC\textsubscript{50} value for hERG current inhibition by axitinib is considered \( \geq 3 \mu M \), providing a safety margin \( \geq 8000\)-fold the human clinical exposure based on C\text{max} at the recommended human starting dose.

TOXICOLOGY

The nonclinical toxicologic profile of axitinib has been extensively investigated, as shown in Table 6.
### Table 6. Key Responses in Toxicology Studies with Axitinib

#### Single-Dose Toxicity

<table>
<thead>
<tr>
<th>Species/Strain</th>
<th>Duration</th>
<th>Dose&lt;sup&gt;a&lt;/sup&gt; (mg/kg/day)</th>
<th>Key Response(s)</th>
<th>NOAEL (mg/kg/day)</th>
<th>LOAEL (mg/kg/day)</th>
<th>Safety Margin&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse/CD-1</td>
<td>1 day</td>
<td>2000&lt;sup&gt;c&lt;/sup&gt;</td>
<td>None observed</td>
<td>2000</td>
<td>&gt;2000</td>
<td>NC</td>
</tr>
<tr>
<td>Dog/Beagle</td>
<td>1 day</td>
<td>2000&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Fecal changes (nonformed, mucoid, discolored)</td>
<td>2000</td>
<td>&gt;2000</td>
<td>19.1</td>
</tr>
</tbody>
</table>

#### Repeat-Dose Toxicity

<table>
<thead>
<tr>
<th>Species/Strain</th>
<th>Duration</th>
<th>Dose&lt;sup&gt;a&lt;/sup&gt; (mg/kg/day)</th>
<th>Key Response(s)</th>
<th>NOAEL (mg/kg/day)</th>
<th>LOAEL (mg/kg/day)</th>
<th>Safety Margin&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse/CD-1</td>
<td>14 days</td>
<td>50</td>
<td>Decreased body weight gain</td>
<td>250 (M)/250 (F)</td>
<td>500 (M)/250 (F)</td>
<td>351.2 (M)/23.5 (F)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250</td>
<td>Decreased reticulocytes and thymus weights</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>500</td>
<td>Mortality; decreased red blood cell parameters; decreased testis/epididymis weights</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>None observed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse/CD-1</td>
<td>28 days</td>
<td>10</td>
<td>None observed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>Increased MCH, MCV, reticulocytes; thickened growth plate</td>
<td>10</td>
<td>30</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250</td>
<td>Testicular atrophy/degeneration; absence of corpora lutea.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Incisor tooth odontopathy; decreased corpora lutea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse/CD-1</td>
<td>13 or 26 weeks&lt;sup&gt;d&lt;/sup&gt;</td>
<td>30</td>
<td>Decreased red blood cells; hyperplasia, inflammation of cecal mucosa</td>
<td>&lt;10</td>
<td>10</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>Mortality; hypospermia in the testes; thickened growth plate; uterine atrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOAEL =** No observed adverse effect level; **LOAEL =** Lowest observed adverse effect level (defined as the dose immediately above the NOAEL dose); **NC =** Not calculated; **M =** Male; **F =** Female; **MCH =** Mean corpuscular hemoglobin; **MCV =** Mean corpuscular volume.

<sup>a</sup> Total daily dose; twice daily (BID) dose delivered approximately 6 hours apart, unless otherwise indicated.

<sup>b</sup> Safety margin calculated as [total AUC<sub>NOAEL, NOEL</sub>/total AUC of 265 ng•h/mL at the recommended human dose of 5 mg BID]; AUC exposures in animals were obtained near termination unless otherwise noted.

<sup>c</sup> Single dose administration followed by a 14-day observation period.

<sup>d</sup> Study included a 4-week recovery period following 13 weeks of dosing.
Table 6. Key Responses in Toxicology Studies with Axitinib (cont’d)

<table>
<thead>
<tr>
<th>Species/ Strain</th>
<th>Duration</th>
<th>Dose</th>
<th>Key Response(s)</th>
<th>NOAEL</th>
<th>LOAEL</th>
<th>Safety Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog/ Beagle</td>
<td>14 days</td>
<td>25/50</td>
<td>Decreased body weight; oral mucosal erythema.</td>
<td>25/50</td>
<td>50/100</td>
<td>12.5f</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50/100</td>
<td>Dark areas on the intestinal mucosa, rectum, stomach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>150/300</td>
<td>Mortality; decreased reticulocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog/ Beagle</td>
<td>28 days</td>
<td>10</td>
<td>Abnormal feces (discolored); delayed sexual maturity, absence of corpora lutea or small follicles</td>
<td>&lt;10</td>
<td>10</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Dog/ Beagle</td>
<td>28 days</td>
<td>30</td>
<td>Decreased reticulocytes; inflammation/ulceration of oral mucosa and tongue; gastrointestinal hemorrhage, inflammation, fibrinoid necrosis of vessels; thickened growth plate; pancreatic zymogen granule depletion with acinar cell proliferation or increased acinar cell apoptosis; Mortality; bone marrow hypocellularity; multinucleated giant cells in testes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog/ Beagle</td>
<td>13 or 26 weeksd</td>
<td>6</td>
<td>Abnormal feces (nonformed, mucoid, liquid, discolored)</td>
<td>6</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>Dog/ Beagle</td>
<td>39 weeksg</td>
<td>1 (M)</td>
<td>Increased incidence of fecal abnormalities</td>
<td>1 (M)/</td>
<td>3 (M)/</td>
<td>0.02 (M)/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 (M)</td>
<td>Decreased testis weights, testicular degeneration/atrophy and syncytial cells; epididymal luminal cellular debris</td>
<td>6 (F)</td>
<td>&gt;6 (F)</td>
<td>0.6 (F)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 (M)</td>
<td>Epididymal hyposperma</td>
<td>6 (F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 (F)</td>
<td>Increased incidence of fecal abnormalities</td>
<td>6 (F)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOAEL = No observed adverse effect level; LOAEL = Lowest observed adverse effect level (defined as the dose immediately above the NOAEL); M = Male; F = Female.

a Total daily dose; twice daily (BID) dose delivered approximately 6 hours apart, unless otherwise indicated.
b Safety margin calculated as \( \frac{\text{total AUC}_{\text{NOAEL, NOEL}}}{\text{total AUC of 265 ng•h/mL at the recommended human dose of 5 mg BID}} \); AUC exposures in animals were obtained near termination unless otherwise noted.
c Study included a 4-week recovery period following 13 weeks of dosing.
d X/Y where X = the dose delivered from Day 1 through the first dose of Day 9 and Y = the dose delivered from the second dose of Day 9 until the end of the treatment period on Day 14.
e Safety margin calculated based on Day 1 AUC exposure values in animals.
g Study included an 8-week recovery period following 39 weeks of dosing.
### Table 6. Key Responses in Toxicology Studies with Axitinib (cont’d)

**Reproductive and Developmental Toxicity**

#### Male Reproduction and Fertility

<table>
<thead>
<tr>
<th>Species/Strain</th>
<th>Duration (days)</th>
<th>Dose (mg/kg/day)</th>
<th>Key Response(s)</th>
<th>NOAEL (mg/kg/day)</th>
<th>LOAEL (mg/kg/day)</th>
<th>Safety Margin b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse/CD-1</td>
<td>≥70</td>
<td>10</td>
<td>Reduced sperm density</td>
<td>&lt;10</td>
<td>10</td>
<td>&lt;3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>Reduced sperm density (statistically significant)</td>
<td>&lt;10</td>
<td>30</td>
<td>&lt;10.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>Reduced sperm count, reduced testes weights</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Female Reproduction and Fertility

<table>
<thead>
<tr>
<th>Species/Strain</th>
<th>Duration (days)</th>
<th>Dose (mg/kg/day)</th>
<th>Key Response(s)</th>
<th>NOAEL (mg/kg/day)</th>
<th>LOAEL (mg/kg/day)</th>
<th>Safety Margin b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse/CD-1</td>
<td>≥15</td>
<td>30</td>
<td>Decreased fertility and embryonic viability</td>
<td>&lt;30</td>
<td>30</td>
<td>&lt;10.8</td>
</tr>
</tbody>
</table>

#### Embryo-fetal Development

<table>
<thead>
<tr>
<th>Species/Strain</th>
<th>Duration (DG)</th>
<th>Dose (mg/kg/day)</th>
<th>Key Response(s)</th>
<th>NOAEL (mg/kg/day)</th>
<th>LOAEL (mg/kg/day)</th>
<th>Safety Margin b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse/CD-1</td>
<td>DG6 to 17</td>
<td>1</td>
<td>Reversible delays in ossification within historical control range</td>
<td>1b</td>
<td>3b</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Cleft palate, common variations in skeletal ossification</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOAEL = No observed adverse effect level; LOAEL = Lowest observed adverse effect level (defined as the dose immediately above the NOAEL); DG = Day of gestation.
a Total daily dose; twice daily (BID) dose delivered approximately 6 hours apart, unless otherwise indicated.
b Safety margin calculated as [total AUC_{NOAEL, NOEL}/total AUC of 265 ng•h/mL at the recommended human dose of 5 mg BID]; AUC exposures in animals were obtained near termination unless otherwise noted.
h Based on developmental not maternal effects.

### Single Dose Toxicity

Axitinib was well-tolerated following single-dose administration in the mouse and dog at dosages up to 2000 mg/kg, as evidenced by the lack of any adverse effects during a 14-day observation period.

### Repeat Dose Toxicity

The primary toxicities following repeat-dose administration were observed in the gastrointestinal, hematopoietic, musculoskeletal (physeal dysplasia and dental caries), and reproductive organs of the mouse and dog, where the axitinib effect on vascular beds was often reflected (see Table 6). Gastrointestinal toxicities (hemorrhage, inflammation, fibrinoid necrosis of vessels) in the dog were accompanied clinically by increased incidences of abnormal fecal excretions, though increases in fecal abnormalities were also observed in the dog without accompanying microscopic findings. Gastrointestinal effects in the mouse were characterized by mucosal hyperplasia and inflammation in the cecum and colon following 6 months of dosing. Hematopoietic effects primarily reflected an effect on the erythron, and were observed in studies of ≥14 days duration in the mouse and dog. Physeal dysplasia was observed in immature mice and dogs given axitinib for at least 1 month, and dental caries were observed in mice treated for more than 1 month. Male reproductive organ effects were identified in the testes/epididymis.
(decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms) in mice and dogs. 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. Partial to full reversibility was demonstrated for the gastrointestinal, hematopoietic, musculoskeletal, and reproductive toxicities observed following 13 or 39 weeks of dosing. Safety margins associated with the primary toxicities were identified in the therapeutic or sub-therapeutic range.

Reproductive and Developmental Toxicities

Male and Female Reproduction and Fertility

Axitinib has the potential to impair reproductive function and fertility in humans. Axitinib did not affect mating or fertility in male mice at any dose tested following at least 70 days of treatment with axitinib. However, reduced testicular weights, sperm density and count were noted following at least 70 days of treatment. In female mice, reduced fertility and embryonic viability were observed at all doses tested following at least 15 days of treatment with axitinib. As shown in Table 6, the no observed adverse effect level (NOAEL) for these findings was not identified.

Embryo-fetal Development

Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate and common variations in skeletal ossification at sub-therapeutic exposures (see Table 6).

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; however, axitinib was shown to be an aneugen in the in vivo mouse bone marrow micronucleus test at AUC exposures >18350 ng·h/mL.
REFERENCES


PART III: CONSUMER INFORMATION

PRINLYTA®
(axitinib tablets)

This leaflet is part III of a three-part "Product Monograph" published when INLYTA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INLYTA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

INLYTA is used in the treatment of adult patients with metastatic (the spread of cancer to other parts of the body) kidney cancer (Renal Cell Carcinoma or RCC) who have had other treatments.

What it does:

INLYTA specifically targets the activity of certain enzymes called tyrosine kinases that play a major role in transmitting the chemical signals required for critical cellular processes. INLYTA prevents growth of blood vessels from surrounding tissue to a solid tumor, and prevents the growth of cancer cells.

When it should not be used:

Do not take INLYTA:

- If you are allergic (hypersensitive) to axitinib or any of the other ingredients of INLYTA, listed under “What the nonmedicinal ingredients are:”

What the medicinal ingredient is:

axitinib

What the nonmedicinal ingredients are:

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

What dosage forms it comes in:

INLYTA is available as oral tablets containing 1 mg, 3 mg, 5 mg, or 7 mg of axitinib.

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

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

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

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

INLYTA should be prescribed and managed by a doctor experienced in the use of cancer drugs.

INLYTA has not been studied in patients with severely reduced liver function (severe hepatic impairment).

Possible serious side effects with INLYTA include:

- high blood pressure and high blood pressure crisis
- blood clots in the vein or the artery
- bleeding (in the brain, respiratory and gastrointestinal tract)
- gastrointestinal perforation (a tear in the stomach or intestine wall) that may result in death
- reversible posterior leukoencephalopathy syndrome, symptoms include headache, confusion, seizures, and visual loss.
- heart problems that may lead to death.

BEFORE you use INLYTA talk to your doctor or pharmacist:

- If you have high blood pressure and its complications, including separation of the layers of the arterial wall (Artery Dissection).
- If you have thyroid gland problems.
- If you have had a recent problem with blood clots in your veins or arteries (types of blood vessels) including stroke, heart attack, embolism, or thrombosis.
- If you have bleeding problems.
- If you have an unhealed wound following surgery or if you have surgery scheduled.
- If you have liver or kidney problems.
- If you have gastrointestinal disorders.
- If you have neurological disorders.
- If you have heart problems.
- If you are pregnant or planning to become pregnant. INLYTA may affect male and female fertility.
- If you are breast-feeding or planning to breast-feed. It is not known if INLYTA passes into your breast milk. You and your doctor should decide if you will take INLYTA or breast-feed. You should not do both.
- If you have a rare hereditary problem of lactose intolerance.

Use in children (under 18 years):

INLYTA is not recommended for use in children since it has not been studied in children under 18 years of age.

Contraception:

- INLYTA may cause birth defects.
Interactions with this medication

Taking other medicines:
Tell your doctor if you are taking other drugs, including prescription and non-prescription, vitamins, and herbal products. INLYTA and certain other medicines can interact with each other and cause serious side effects.

Especially tell your doctor if you take:
- Dexamethasone (a steroid).
- Medicine for: asthma, tuberculosis (TB), seizures (epilepsy), bacterial infections (antibiotics), fungal infections (antifungals), depression, or HIV (AIDS).
- Herbal medicines (such as St. John’s wort).
- Antacids, such as rabeprazole, which should be avoided 2 hours before and 2 hours after taking INLYTA.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine. Do not take other medicines with INLYTA until you have talked with your doctor.

Also, do not drink grapefruit juice or eat grapefruit as they may change the amount of INLYTA in your body.

Proper use of this medication

Usual dose:
Take INLYTA exactly as prescribed by your doctor.
Usual Starting Dose: 5 mg taken by mouth twice a day with or without food.
Maximum dose: 10 mg twice daily.
Swallow the tablet whole with a glass of water.

Do not drink grapefruit juice or eat grapefruit as they may change the amount of INLYTA in your body.

Overdose:
If you think you may have accidentally taken too many INLYTA tablets, immediately contact your doctor, or poison control centre, or go to the emergency room of the nearest hospital even if there are no symptoms.

Missed Dose:
If you vomit or miss a dose of INLYTA, don’t take an additional dose. Take the next dose at the usual time. Call your doctor right away if you take too much INLYTA.

Side effects and what to do about them

INLYTA may cause the following serious side effects:
- High blood pressure
- Decreased thyroid function (hypothyroidism)
- Increased bleeding problem
- Blood clot in the veins, arteries, or lungs
- Tear in the intestinal wall (perforation of the bowel)

Very common side effects (these are likely to affect more than or equal to 1 in every 10 people):
- decreased thyroid gland function (hypothyroidism) with symptoms such as fatigue, constipation, dry skin, weight gain
- diarrhea (frequent or loose bowel movements)
- nausea
- vomiting
- constipation
- soreness of the mouth, tongue, or throat
- abdominal pain
- upset stomach
- tiredness or feeling weak
- hoarseness (disorder of the voice)
- decreased appetite
- decreased weight
- joint pain
- pain in extremity
- headache
- taste disturbance
- protein in urine
- cough
- breathlessness
- rash, redness, itching or peeling of your skin (hand-foot syndrome)
- dry skin
- itchy skin
- hair loss
- redness of skin
- high blood pressure
- bleeding problems (nosebleed, blood in urine, rectal bleeding, coughing up blood)

Common side effects (these are likely to affect more than or equal to 1 but less than 10 in every 100 people):
- dizziness
- upper stomach pain
- muscle pain
- dehydration
- decreased amount of red blood cells in the blood
- hemorrhoids
- ringing in the ears
- increase in lipase (an enzyme from the pancreas)
- blood clot in the lung
- formation of blood clot in deep vein
- some vascular disorders of the retina
- increased red blood cells in the blood
- transient stroke-like episodes
• increased thyroid gland function (hyperthyroidism) with symptoms such as rapid weight loss, sweating, faster heartbeat
• excess bilirubin in blood with symptoms such as yellow coloring of the skin
• painful tongue
• kidney failure
• heart problems

Uncommon side effects (these are likely to affect more than or equal to 0.1 but less than 1 in every 100 people):

• severe and rapid increase in blood pressure (hypertensive crisis)
• loss of monocular vision (retinal artery occlusion)
• a neurological disorder called reversible posterior leukoencephalopathy syndrome with symptoms such as headache, seizures, lethargy, confusion, blindness and other visual disturbances

Tell your doctor if you have any side effects that bother you or that do not go away. These are not all the side effects with INLYTA. Ask your doctor or pharmacist for more information.

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist</th>
<th>Stop taking drug and call your doctor or pharmacist</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Common</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high blood pressure</td>
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<tr>
<td>bleeding problems (nosebleed, blood in urine, rectal bleeding, coughing up blood)</td>
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<tr>
<td><strong>Common</strong></td>
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<tr>
<td>Heart problems (cardiomyopathy) with symptoms such as shortness of breath, fatigue, and swollen feet, ankles, legs and abdomen</td>
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<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td>decreased thyroid gland function (hypothyroidism) with symptoms such as fatigue, constipation, dry skin, weight gain</td>
<td>√</td>
<td></td>
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<tr>
<td>problem with blood clots in your veins or arteries (types of blood vessels)</td>
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<tr>
<td>perforation of the bowel (tear in your intestinal wall)</td>
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</tbody>
</table>

This is not a complete list of side effects. For any unexpected effects while taking INLYTA, contact your doctor or pharmacist.

**HOW TO STORE IT**

• Store INLYTA tablets at a controlled room temperature of 25°C (excursions permitted to 15 - 30°C).
• Store in the original package.
• Do not use after the expiry date (EXP) shown on the outer pack and label.
• Do not use any pack that is damaged or shows signs of tampering.
• Keep INLYTA, and all other medicines, out of the reach and sight of children.
• As with all medicines, INLYTA should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of the medicines no longer required. These measures will help to protect the environment.
REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at: www.pfizer.ca or can be obtained by contacting the sponsor, Pfizer Canada ULC, at: 1-800-463-6001 (Medical Information)

This leaflet was prepared by Pfizer Canada ULC.

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