HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INLYTA safely and effectively. See full prescribing information for INLYTA.

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

----------RECENT MAJOR CHANGES----------

Indications and Usage, First-line advanced RCC (1.1)	6/2020
Dosage and Administration, Recommended Dosing (2.1)	6/2020
Dosage and Administration, Dose Modification Guidelines (2.2)	6/2020
Warnings and Precautions, Risk of Impaired Wound Healing (5.8)	1/2020
Warnings and Precautions, Hepatotoxicity (5.11)	6/2020
Warnings and Precautions, Major Adverse Cardiovascular Events (MACE) (5.13)	6/2020

---------- INDICATIONS AND USAGE----------

INLYTA is a kinase inhibitor indicated:

- in combination with avelumab, for the first-line treatment of patients with advanced renal cell carcinoma (RCC). (1.1)
- in combination with pembrolizumab, for the first-line treatment of patients with advanced RCC. (1.1)
- as a single agent, for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- INLYTA 5 mg orally twice daily with avelumab 800 mg every 2 weeks. (2.1)
- INLYTA 5 mg orally twice daily with pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks. (2.1)
- INLYTA as a single agent the starting dose is 5 mg orally twice daily. (2.1)
- Dose adjustments can be made based on individual safety and tolerability. (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)
- For patients with moderate hepatic impairment, decrease the starting dose by approximately half. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------

1 mg and 5 mg tablets (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Hypertension and Hypertensive Crisis: 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 anti-hypertensive medications, reduce the INLYTA dose. (5.1)
- Arterial and Venous Thromboembolic Events: Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk for these events. (5.2, 5.3)
- Hemorrhage: 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. (5.4)
- Cardiac Failure: Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. (5.5)
- Gastrointestinal Perforation and Fistula Formation: Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. (5.6)
- Hypothyroidism: Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment with INLYTA. (5.7)
- Risk of Impaired Wound Healing: Withhold INLYTA for at least 2 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of INLYTA after resolution of wound healing complications has not been established. (5.8)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS has been observed. Permanently discontinue INLYTA if signs or symptoms of RPLS occur. (5.9)
- Proteinuria: Monitor for proteinuria before initiation of, and periodically throughout, treatment with INLYTA. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment with INLYTA. (5.10)
- Hepatotoxicity: Liver enzyme elevation has occurred during treatment with INLYTA as a single agent. Monitor ALT, AST and bilirubin before initiation of, and periodically throughout, treatment with INLYTA. When used in combination with avelumab or pembrolizumab, higher frequencies of Grade 3 and 4 ALT and AST elevation may occur. Consider more frequent monitoring of liver enzymes. Consider withholding INLYTA and/or avelumab or pembrolizumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity. (5.11)
- Use in Patients with Hepatic Impairment: Decrease the starting dose of INLYTA if used in patients with moderate hepatic impairment. INLYTA has not been studied in patients with severe hepatic impairment. (2.2, 5.12)
- Major adverse cardiovascular events (INLYTA in combination with avelumab): Optimize management of cardiovascular risk factors. Discontinue INLYTA in combination with avelumab for Grade 3-4 events. (5.13)
- Embryo-Fetal Toxicity: INLYTA can cause fetal harm. Advise patients of the potential risk to the fetus and to use effective contraception. (5.14, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (≥20%) are:

INLYTA in combination with avelumab: diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain, and headache. (6.1)

INLYTA in combination with pembrolizumab: diarrhea, fatigue/asthenia, hypertension, hypothyroidism, decreased appetite, hepatotoxicity, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. (6.1)

INLYTA as a single agent: diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, 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. If unavoidable, reduce the INLYTA dose. (2.2, 7.1)
- Avoid strong CYP3A4/5 inducers. (7.2)

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed. (8.2)

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

Revised: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 First-Line Advanced Renal Cell Carcinoma

INLYTA in combination with avelumab is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

INLYTA in combination with pembrolizumab is indicated for the first-line treatment of patients with advanced renal cell carcinoma.

1.2 Second-Line Advanced Renal Cell Carcinoma

INLYTA as a single agent is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

First-Line Advanced RCC

The recommended dose of INLYTA is 5 mg orally taken twice daily (12 hours apart) with or without food in combination with avelumab 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. When INLYTA is used in combination with avelumab, dose escalation of INLYTA above the initial 5 mg dose may be considered at intervals of two weeks or longer. Review the Full Prescribing Information for recommended avelumab dosing information.

The recommended dose of INLYTA is 5 mg orally twice daily (12 hours apart) with or without food in combination with pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity. When INLYTA is used in combination with pembrolizumab, dose escalation of INLYTA above the initial 5 mg dose may be considered at intervals of six weeks or longer. Review the Full Prescribing Information for recommended pembrolizumab dosing information.

Second-Line Advanced RCC

When INLYTA is used as a single agent, the recommended starting oral dose is 5 mg twice daily. Administer INLYTA doses approximately 12 hours apart with or without food.

Important Administration Instructions

Advise patients to swallow INLYTA whole with a full glass of water. If the patient vomits or misses a dose, an additional dose should not be taken. Advise the patient to take the next prescribed dose at the usual time.

2.2 Dose Modification Guidelines

Dose increase or reduction is recommended based on individual safety and tolerability.

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

Over the course of treatment, management of some adverse drug reactions may require temporary interruption or permanent discontinuation and/or dose reduction of INLYTA therapy *[see Warnings and Precautions (5)]*. If dose reduction from 5 mg twice daily is required, the recommended dose is 3 mg twice daily. If additional dose reduction is required, the recommended dose is 2 mg twice daily.

Strong CYP3A4/5 Inhibitors

The concomitant use of strong CYP3A4/5 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although INLYTA dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of INLYTA by approximately half is recommended, as this dose reduction is predicted to adjust the axitinib area under the plasma concentration vs time curve (AUC) to the range observed without inhibitors. The subsequent doses can be increased or decreased based on individual safety and tolerability. If co-administration of the strong inhibitor is discontinued, the INLYTA dose should be returned (after 3 – 5 half-lives of the inhibitor) to that used prior to initiation of the strong CYP3A4/5 inhibitor *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

Hepatic Impairment

No starting dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). Based on the pharmacokinetic data, the INLYTA starting dose should be reduced by approximately half in patients with baseline moderate hepatic impairment (Child-Pugh class B). The subsequent doses can be increased or decreased based on individual safety and tolerability. INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C) *[see Warnings and Precautions (5.12), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Hepatotoxicity

In patients being treated with INLYTA in combination with avelumab:

- If ALT or AST ≥3 times ULN but <5 times ULN or total bilirubin ≥1.5 times ULN but <3 times ULN, withhold both INLYTA and avelumab until these adverse reactions recover to Grades 0-1. If persistent (greater than 5 days), consider corticosteroid therapy [initial dose of 0.5 to 1 mg/kg/day] prednisone or equivalent followed by a taper. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with INLYTA, consider dose reduction as per recommended dose modification guidelines.

- If ALT or AST ≥5 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN or total bilirubin ≥3 times ULN, permanently discontinue both INLYTA and avelumab and consider corticosteroid therapy [initial dose 1 to 2 mg/kg/day prednisone or equivalent followed by a taper].

Review the Full Prescribing Information for additional dose modifications for avelumab.

In patients being treated with INLYTA in combination with pembrolizumab:

- If ALT or AST ≥3 times ULN but <10 times ULN without concurrent total bilirubin ≥2 times ULN, withhold both INLYTA and pembrolizumab until these adverse reactions recover to Grades 0-1. Consider corticosteroid therapy. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with INLYTA, consider dose reduction as per recommended dose modification guidelines.
- If ALT or AST ≥10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN, permanently discontinue both INLYTA and pembrolizumab and consider corticosteroid therapy.

Review the Full Prescribing Information for additional dose modifications for pembrolizumab.

3 DOSAGE FORMS AND STRENGTHS

- 1 mg tablets of INLYTA: red, film-coated, oval tablets, debossed with “Pfizer” on one side and “1 XNB” on the other side.
- 5 mg tablets of INLYTA: red, film-coated, triangular tablets, debossed with “Pfizer” on one side and “5 XNB” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension and Hypertensive Crisis

In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving INLYTA and 103/355 patients (29%) receiving sorafenib. Grade 3/4 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%) receiving INLYTA and none of the patients receiving sorafenib. The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of INLYTA treatment and blood pressure increases have been observed as early as 4 days after starting INLYTA. Hypertension was managed with standard anti-hypertensive therapy. Discontinuation of INLYTA treatment due to hypertension occurred in 1/359 patients (<1%) receiving INLYTA and none of the patients 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 receiving anti-hypertensive medications should be monitored for hypotension *[see Dosage and Administration (2.2)]*.

5.2 Arterial Thromboembolic Events

In clinical trials, arterial thromboembolic events have been reported, including deaths. In a controlled clinical study with INLYTA for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving INLYTA and 4/355 patients (1%) receiving sorafenib. Fatal cerebrovascular accident was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib *[see Adverse Reactions (6.1)]*.

In clinical trials with INLYTA, arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion) were reported in 17/715 patients (2%), 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 an arterial 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 controlled clinical study with INLYTA for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving INLYTA and 2/355 patients (1%) receiving sorafenib. Grade 3/4 venous thromboembolic events were reported in 9/359 patients (3%) receiving INLYTA (including pulmonary embolism, deep vein thrombosis, retinal vein occlusion and retinal vein thrombosis) and 2/355 patients (1%) receiving sorafenib. Fatal pulmonary embolism was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical trials with INLYTA, venous thromboembolic events were reported in 22/715 patients (3%), with two deaths secondary to pulmonary embolism.

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.

5.4 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, hematuria, hemoptysis, lower gastrointestinal hemorrhage, and melena) and 11/355 (3%) patients receiving sorafenib. Fatal hemorrhage was reported in 1/359 patients (<1%) receiving INLYTA (gastric hemorrhage) and 3/355 patients (1%) receiving sorafenib.

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.

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 1/355 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.

5.6 Gastrointestinal Perforation and Fistula Formation

In a controlled clinical study with INLYTA for the treatment of patients with RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical trials with INLYTA, gastrointestinal perforation was reported in 5/715 patients (1%), including one death. In addition to cases of gastrointestinal perforation, fistulas were reported in 4/715 patients (1%).

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

5.7 Thyroid Dysfunction

In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypothyroidism was reported in 69/359 patients (19%) receiving INLYTA and 29/355 patients (8%) receiving sorafenib. Hyperthyroidism was reported in 4/359 patients (1%) receiving INLYTA and 4/355 patients (1%) receiving sorafenib. In patients who had thyroid stimulating hormone (TSH) <5 μU/mL before treatment, elevations of TSH to ≥10 μU/mL occurred in 79/245 patients (32%) receiving INLYTA and 25/232 patients (11%) receiving sorafenib *[see Adverse Reactions (6.1)]*.

Monitor thyroid function before initiation of, and periodically throughout, treatment with INLYTA. Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain euthyroid state.

5.8 Risk of Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, INLYTA has the potential to adversely affect wound healing.

Withhold INLYTA for at least 2 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of INLYTA after resolution of wound healing complications has not been established.

5.9 Reversible Posterior Leukoencephalopathy Syndrome

In a controlled clinical study with INLYTA for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib *[see Adverse Reactions (6.1)]*. There were two additional reports of RPLS in other clinical trials with INLYTA.

RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS. Discontinue INLYTA in patients developing RPLS. The safety of reinitiating INLYTA therapy in patients previously experiencing RPLS is not known.

5.10 Proteinuria

In a controlled clinical study with INLYTA for the treatment of patients with RCC, proteinuria was reported in 39/359 patients (11%) receiving INLYTA and 26/355 patients (7%) receiving sorafenib. Grade 3 proteinuria was reported in 11/359 patients (3%) receiving INLYTA and 6/355 patients (2%) receiving sorafenib *[see Adverse Reactions (6.1)]*.

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

5.11 Hepatotoxicity

INLYTA as a Single Agent

In a controlled clinical study with INLYTA for the treatment of patients with RCC, alanine aminotransferase (ALT) elevations of all grades occurred in 22% of patients on both arms, with Grade 3/4 events in <1% of patients on the INLYTA arm. When used as a single agent, monitor ALT, aspartate aminotransferase (AST) and bilirubin before initiation of and periodically throughout treatment with INLYTA.

INLYTA in Combination with Avelumab or with Pembrolizumab

INLYTA in combination with avelumab or with pembrolizumab can cause hepatotoxicity with higher than expected frequencies of Grade 3 and 4 ALT and AST elevation. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy.

With the combination of INLYTA and avelumab, Grades 3 and 4 increased ALT and increased AST were reported in 9% and 7% of patients, respectively. In patients with ALT ≥3 times ULN (Grades 2-4, n=82), ALT resolved to Grades 0-1 in 92%. Among the 73 patients who were rechallenged with either avelumab (59%) or axitinib (85%) monotherapy or with both (55%), 66% had no recurrence of ALT ≥3 times ULN.

With the combination of INLYTA and pembrolizumab, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. The median time to onset of increased ALT was 2.3 months (range: 7 days to 19.8 months). Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either pembrolizumab (3%) or axitinib (31%) administered as a single agent or with both (50%), 55% had no recurrence of ALT >3 times ULN.

Withhold INLYTA and avelumab for moderate (Grade 2) hepatotoxicity and permanently discontinue the combination for severe or life-threatening (Grade 3 or 4) hepatotoxicity. Administer corticosteroids as needed *[see avelumab full prescribing information]*.

For elevated liver enzymes, interrupt INLYTA and pembrolizumab and consider administering corticosteroids as needed *[see pembrolizumab full prescribing information]*.

5.12 Use in Patients with Hepatic Impairment

The systemic exposure to axitinib was higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering INLYTA to patients with moderate hepatic impairment (Child-Pugh class B). INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C) *[see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

5.13 Major Adverse Cardiovascular Events (MACE)

INLYTA in combination with avelumab can cause severe and fatal cardiovascular events. Consider baseline and periodic evaluations of left ventricular ejection fraction. Monitor for signs and symptoms of cardiovascular events. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue INLYTA and avelumab for Grade 3-4 cardiovascular events.

MACE occurred in 7% of patients with advanced RCC treated with INLYTA in combination with avelumab compared to 3.4% treated with sunitinib in a randomized trial, JAVELIN Renal 101. These events included death due to cardiac events (1.4%), Grade 3-4 myocardial infarction (2.8%), and Grade 3-4 congestive heart failure (1.8%). Median time to onset of MACE was 4.2 months (range: 2 days to 24.5 months).

5.14 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, INLYTA can cause fetal harm when administered to a pregnant woman. There are no available human data to inform the drug-associated risk. 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. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with INLYTA and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with INLYTA and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

When INLYTA is used in combination with avelumab or pembrolizumab, refer to the full prescribing information of avelumab or pembrolizumab for pregnancy and contraception information.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling *[see Warnings and Precautions (5)]*:

- Hypertension and hypertensive crisis *[see Warnings and Precautions (5.1)]*
- Arterial thromboembolic events *[see Warnings and Precautions (5.2)]*
- Venous thromboembolic events *[see Warnings and Precautions (5.3)]*
- Hemorrhage *[see Warnings and Precautions (5.4)]*
- Cardiac failure *[see Warnings and Precautions (5.5)]*

- Gastrointestinal perforation and fistula formation *[see Warnings and Precautions (5.6)]*
- Thyroid dysfunction *[see Warnings and Precautions (5.7)]*
- Reversible posterior leukoencephalopathy syndrome *[see Warnings and Precautions (5.9)]*
- Proteinuria *[see Warnings and Precautions (5.10)]*
- Hepatotoxicity *[see Warnings and Precautions (5.11)]*
- Hepatic impairment *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trials Experience

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 combination with avelumab in JAVELIN Renal 101 and pembrolizumab in KEYNOTE-426 for the first-line treatment of patients with advanced RCC *[see Clinical Studies (14.1)]*. The data described *[see Adverse Reactions (6.1)]* reflect exposure to INLYTA in combination with avelumab in 434 patients and pembrolizumab in 429 patients *[see Clinical Studies (14.1)]*.

The safety of INLYTA has been evaluated in 715 patients in second-line monotherapy studies, which included 537 patients with advanced RCC. The data described *[see Adverse Reactions (6.1)]* reflect exposure to INLYTA in 359 patients with advanced RCC who participated in a randomized clinical study versus sorafenib *[see Clinical Studies (14.2)]*.

First-Line Advanced RCC

INLYTA in Combination with Avelumab

The safety of INLYTA in combination with avelumab was evaluated in JAVELIN Renal 101. Patients with autoimmune disease other than type I diabetes mellitus, vitiligo, psoriasis, or thyroid disorders not requiring immunosuppressive treatment were excluded. Patients received INLYTA 5 mg twice daily (N=434) in combination with avelumab 10 mg/kg every 2 weeks administered or sunitinib 50 mg once daily for 4 weeks followed by 2 weeks off (N=439).

In the INLYTA plus avelumab arm, 70% were exposed to avelumab for ≥6 months and 29% were exposed for ≥1 year in JAVELIN Renal 101 *[see Clinical Studies (14.1)]*.

The median age of patients treated with INLYTA in combination with avelumab was 62 years (range: 29 to 83), 38% of patients were 65 years or older, 71% were male, 75% were White, and the Eastern Cooperative Oncology Group (ECOG) performance score was 0 (64%) or 1 (36%).

Fatal adverse reactions occurred in 1.8% of patients receiving INLYTA in combination with avelumab. These included sudden cardiac death (1.2%), stroke (0.2%), myocarditis (0.2%), and necrotizing pancreatitis (0.2%).

Serious adverse reactions occurred in 35% of patients receiving INLYTA in combination with avelumab. Serious adverse reactions in ≥1% of patients included diarrhea (2.5%), dyspnea (1.8%), hepatotoxicity (1.8%), venous thromboembolic disease (1.6%), acute kidney injury (1.4%), and pneumonia (1.2%).

Permanent discontinuation due to an adverse reaction of either INLYTA or avelumab occurred in 22% of patients: 19% avelumab only, 13% INLYTA only, and 8% both drugs. The most common adverse reactions (>1%) resulting in permanent discontinuation of avelumab or the combination were hepatotoxicity (6%) and infusion-related reaction (1.8%).

Dose interruptions or reductions due to an adverse reaction, excluding temporary interruptions of avelumab infusions due to infusion-related reactions, occurred in 76% of patients receiving INLYTA in combination with avelumab. This includes interruption of avelumab in 50% of patients. INLYTA was interrupted in 66% and dose reduced in 19% of patients. The most common adverse reaction (>10%) resulting in interruption of avelumab was diarrhea (10%) and the most common adverse reactions resulting in either interruption or dose reduction of INLYTA were diarrhea (19%), hypertension (18%), palmar-plantar erythrodysesthesia (18%), and hepatotoxicity (10%).

The most common adverse reactions (≥20%) in patients receiving INLYTA in combination with avelumab were diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain, and headache.

Forty-eight (11%) of patients treated with INLYTA in combination with avelumab received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5.12)]*.

Table 1 summarizes adverse reactions that occurred in ≥20% of INLYTA in combination with avelumab-treated patients.

Table 1: Adverse Reactions (≥20%) of Patients Receiving INLYTA in Combination with Avelumab (JAVELIN Renal 101 Trial)[1]

Adverse Reactions	INLYTA plus Avelumab (N=434)		Sunitinib (N=439)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal Disorders				
Diarrhea[2]	62	8	48	2.7
Nausea	34	1.4	39	1.6
Mucositis[3]	34	2.8	35	2.1
Hepatotoxicity[4]	24	9	18	3.6
Abdominal pain[5]	22	1.4	19	2.1
General Disorders and Administration Site Conditions				
Fatigue[6]	53	6	54	6
Vascular Disorders				
Hypertension[7]	50	26	36	17
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[8]	40	3.2	33	2.7
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	33	6	34	4
Rash[9]	25	0.9	16	0.5

Adverse Reactions	INLYTA plus Avelumab (N=434)		Sunitinib (N=439)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	31	0.5	3.2	0
Dyspnea[10]	23	3.0	16	1.8
Cough	23	0.2	19	0
Metabolism and Nutrition Disorders				
Decreased appetite	26	2.1	29	0.9
Endocrine Disorders				
Hypothyroidism	25	0.2	14	0.2
Nervous System Disorders				
Headache	21	0.2	16	0.2

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.03 (NCI CTCAE v4).

[1] The trial was not designed to demonstrate a statistically significant difference in the incidence of adverse reactions between avelumab in combination with INLYTA and sunitinib.

[2] Diarrhea is a composite term that includes diarrhea, autoimmune colitis, and colitis

[3] Mucositis is a composite term that includes mucosal inflammation and stomatitis

[4] Hepatotoxicity is a composite term that includes ALT increased, AST increased, autoimmune hepatitis, bilirubin conjugated, bilirubin conjugated increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis fulminant, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, liver disorder, liver injury, and transaminases increased

[5] Abdominal pain is a composite term that includes abdominal pain, flank pain, abdominal pain upper, and abdominal pain lower

[6] Fatigue is a composite term that includes fatigue and asthenia

[7] Hypertension is a composite term that includes hypertension and hypertensive crisis

[8] Musculoskeletal pain is a composite term that includes musculoskeletal pain, musculoskeletal chest pain, myalgia, back pain, bone pain, musculoskeletal discomfort, neck pain, spinal pain, and pain in extremity

[9] Rash is a composite term that includes rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash erythematous, rash papular, and rash pustular

[10] Dyspnea is a composite term that includes dyspnea, dyspnea exertional and dyspnea at rest

Other clinically important adverse reactions that occurred in less than 20% of patients in JAVELIN Renal 101 included arthralgia, weight decreased, and chills.

Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Infusion-related reactions occurred in 12% (Grade 3: 1.6%; no Grade 4) of patients treated with INLYTA in combination with avelumab.

Table 2 summarizes selected laboratory abnormalities that occurred in ≥20% of INLYTA in combination with avelumab-treated patients.

Table 2: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving INLYTA in Combination with Avelumab (JAVELIN Renal 101 Trial)[1]

Laboratory Abnormality	INLYTA plus Avelumab		Sunitinib[2]	
	Any Grade %	Grade 3-4 %	Any Grade %	Grade 3-4 %
Chemistry				
Blood triglycerides increased	71	13	48	5
Blood creatinine increased	62	2.3	68	1.4
Blood cholesterol increased	57	1.9	22	0.7
Alanine aminotransferase increased (ALT)	50	9	46	3.2
Aspartate aminotransferase increased (AST)	47	7	57	3.2
Blood sodium decreased	38	9	37	10
Lipase increased	37	14	25	7
Blood potassium increased	35	3.0	28	3.9
Blood bilirubin increased	21	1.4	23	1.4
Hematology				
Platelet count decreased	27	0.7	80	1.5
Hemoglobin decreased	21	2.1	65	8

[1] The trial was not designed to demonstrate a statistically significant difference in the incidence of laboratory abnormalities between INLYTA in combination with avelumab and sunitinib.
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: INLYTA in combination with avelumab group (range: 413 to 428 patients) and sunitinib group (range: 405 to 433 patients).

INLYTA in Combination with Pembrolizumab

The safety of INLYTA in combination with pembrolizumab was investigated in KEYNOTE-426 *[see Clinical Studies (14.1)]*. Patients with medical conditions that required systemic corticosteroids or other immunosuppressive medications or had a history of severe autoimmune disease other than type 1 diabetes, vitiligo, Sjogren's syndrome, and hypothyroidism stable on hormone replacement were ineligible. Patients received INLYTA 5 mg orally twice daily and pembrolizumab 200 mg intravenously every 3 weeks, or sunitinib 50 mg once daily for 4 weeks and then off treatment for 2 weeks. The median duration of exposure to the combination therapy of INLYTA and pembrolizumab was 10.4 months (range: 1 day to 21.2 months).

The study population characteristics were: median age of 62 years (range: 30 to 89), 40% age 65 or older; 71% male; 80% White; and 80% Karnofsky Performance Status (KPS) of 90-100 and 20% KPS of 70-80.

Fatal adverse reactions occurred in 3.3% of patients receiving INLYTA in combination with pembrolizumab. These included 3 cases of cardiac arrest, 2 cases of pulmonary embolism and 1 case each of cardiac failure, death due to unknown cause, myasthenia gravis, myocarditis, Fournier's gangrene, plasma cell myeloma, pleural effusion, pneumonitis, and respiratory failure.

Serious adverse reactions occurred in 40% of patients receiving INLYTA in combination with pembrolizumab. Serious adverse reactions in ≥1% of patients receiving INLYTA in combination with pembrolizumab included hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonitis (1%).

Permanent discontinuation due to an adverse reaction of either INLYTA or pembrolizumab occurred in 31% of patients; 13% pembrolizumab only, 13% INLYTA only, and 8% both drugs. The most common adverse reaction (>1%) resulting in permanent discontinuation of INLYTA, pembrolizumab, or the combination was hepatotoxicity (13%), diarrhea/colitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%).

Dose interruptions or reductions due to an adverse reaction, excluding temporary interruptions of pembrolizumab infusions due to infusion-related reactions, occurred in 76% of patients receiving pembrolizumab in combination with axitinib. This includes interruption of pembrolizumab in 50% of patients. INLYTA was interrupted in 64% of patients and dose reduced in 22% of patients. The most common adverse reactions (>10%) resulting in either interruption or reduction of INLYTA were hepatotoxicity (21%), diarrhea (19%), and hypertension (18%) and the most common adverse reactions (>10%) resulting in interruption of pembrolizumab were hepatotoxicity (14%) and diarrhea (11%).

The most common adverse reactions (≥20%) in patients receiving INLYTA and pembrolizumab were diarrhea, fatigue/asthenia, hypertension, hypothyroidism, decreased appetite, hepatotoxicity, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation.

Twenty-seven percent (27%) of patients treated with INLYTA in combination with pembrolizumab received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction.

Tables 3 and 4 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in at least 20% of patients treated with INLYTA and pembrolizumab in KEYNOTE-426.

Table 3: Adverse Reactions Occurring in ≥20% of Patients Treated with INLYTA and Pembrolizumab (KEYNOTE-426 Trial)

Adverse Reactions	INLYTA plus Pembrolizumab N=429		Sunitinib N=425	
	All Grades* %	Grades 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Diarrhea†	56	11	45	5
Nausea	28	0.9	32	0.9
Constipation	21	0	15	0.2
General				
Fatigue/Asthenia	52	5	51	10
Vascular				
Hypertension‡	48	24	48	20
Hepatobiliary				
Hepatotoxicity§	39	20	25	4.9
Endocrine				
Hypothyroidism	35	0.2	32	0.2
Metabolism and Nutrition				
Decreased appetite	30	2.8	29	0.7
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	28	5	40	3.8
Stomatitis/Mucosal inflammation	27	1.6	41	4
Rash¶	25	1.4	21	0.7
Respiratory, Thoracic, and Mediastinal				
Dysphonia	25	0.2	3.3	0
Cough	21	0.2	14	0.5

* Graded per NCI CTCAE v4.03

† Includes diarrhea, colitis, enterocolitis, gastroenteritis, enteritis, enterocolitis hemorrhagic

‡ Includes hypertension, blood pressure increased, hypertensive crisis, labile hypertension

§ Includes ALT increased, AST increased, autoimmune hepatitis, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis fulminant, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased

¶ Includes rash, butterfly rash, dermatitis, dermatitis acneform, dermatitis atopic, dermatitis, bullous, dermatitis contact, exfoliative rash, genital rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, seborrheic dermatitis, skin discoloration, skin exfoliation, perineal rash

Table 4: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving INLYTA With Pembrolizumab in KEYNOTE-426

Laboratory Test*	INLYTA plus Pembrolizumab		Sunitinib	
	All Grades† %	Grade 3-4 %	All Grades %	Grade 3-4 %
Chemistry				
Hyperglycemia	62	9	54	3.2
Increased ALT	60	20	44	5
Increased AST	57	13	56	5
Increased creatinine	43	4.3	40	2.4
Hyponatremia	35	8	29	8
Hyperkalemia	34	6	22	1.7
Hypoalbuminemia	32	0.5	34	1.7
Hypercalcemia	27	0.7	15	1.9
Hypophosphatemia	26	6	49	17
Increased alkaline phosphatase	26	1.7	30	2.7
Hypocalcemia‡	22	0.2	29	0.7
Blood bilirubin increased	22	2.1	21	1.9
Activated partial thromboplastin time prolonged§	22	1.2	14	0
Hematology				
Lymphopenia	33	11	46	8
Anemia	29	2.1	65	8
Thrombocytopenia	27	1.4	78	14

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: pembrolizumab/axitinib (range: 342 to 425 patients) and sunitinib (range: 345 to 422 patients).
† Graded per NCI CTCAE v4.03
‡ Corrected for albumin
§ Two patients with a Grade 3 elevated activated partial thromboplastin time prolonged (aPTT) were also reported as having an adverse reaction of hepatotoxicity.

Second-Line Advanced RCC

The median duration of treatment was 6.4 months (range 0.03 to 22.0) for patients who received INLYTA and 5.0 months (range 0.03 to 20.1) for patients who received sorafenib. Dose modifications or temporary delay of treatment due to an adverse reaction occurred in 199/359 patients (55%) receiving INLYTA and 220/355 patients (62%) receiving sorafenib. Permanent discontinuation due to an adverse reaction occurred in 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 5 presents adverse reactions reported in ≥10% patients who received INLYTA or sorafenib.

Table 5: Adverse Reactions Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib

Adverse Reaction[a]	INLYTA (N=359)		Sorafenib (N=355)	
	All Grades[b]	Grade 3/4	All Grades[b]	Grade 3/4
	%	%	%	%
Diarrhea	55	11	53	7
Hypertension	40	16	29	11
Fatigue	39	11	32	5
Decreased appetite	34	5	29	4
Nausea	32	3	22	1
Dysphonia	31	0	14	0
Palmar-plantar erythrodysesthesia syndrome	27	5	51	16
Weight decreased	25	2	21	1
Vomiting	24	3	17	1
Asthenia	21	5	14	3
Constipation	20	1	20	1
Hypothyroidism	19	<1	8	0
Cough	15	1	17	1
Mucosal inflammation	15	1	12	1
Arthralgia	15	2	11	1
Stomatitis	15	1	12	<1
Dyspnea	15	3	12	3
Abdominal pain	14	2	11	1
Headache	14	1	11	0
Pain in extremity	13	1	14	1
Rash	13	<1	32	4
Proteinuria	11	3	7	2
Dysgeusia	11	0	8	0
Dry skin	10	0	11	0
Dyspepsia	10	0	2	0
Pruritus	7	0	12	0
Alopecia	4	0	32	0
Erythema	2	0	10	<1

[a] Percentages are treatment-emergent, all-causality events

[b] 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%), lipase increased (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 6 presents the most common laboratory abnormalities reported in ≥10% patients who received INLYTA or sorafenib.

Table 6: Laboratory Abnormalities Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib

Laboratory Abnormality	N	INLYTA		N	Sorafenib	
		All Grades[a]	Grade 3/4		All Grades[a]	Grade 3/4
		%	%		%	%
Hematology						
Hemoglobin decreased	320	35	<1	316	52	4
Lymphocytes (absolute) decreased	317	33	3	309	36	4
Platelets decreased	312	15	<1	310	14	0
White blood cells decreased	320	11	0	315	16	<1
Chemistry						
Creatinine increased	336	55	0	318	41	<1
Bicarbonate decreased	314	44	<1	291	43	0
Hypocalcemia	336	39	1	319	59	2
ALP increased	336	30	1	319	34	1
Hyperglycemia	336	28	2	319	23	2
Lipase increased	338	27	5	319	46	15
Amylase increased	338	25	2	319	33	2
ALT increased	331	22	<1	313	22	2
AST increased	331	20	<1	311	25	1
Hypernatremia	338	17	1	319	13	1
Hypoalbuminemia	337	15	<1	319	18	1
Hyperkalemia	333	15	3	314	10	3
Hypoglycemia	336	11	<1	319	8	<1
Hyponatremia	338	13	4	319	11	2
Hypophosphatemia	336	13	2	318	49	16

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

Selected laboratory abnormalities (all grades) that were reported in <10% of patients treated with INLYTA included hemoglobin increased (above the upper limit of normal) (9% for INLYTA versus 1% for sorafenib) and hypercalcemia (6% for INLYTA versus 2% for sorafenib).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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.

Vascular disorders: arterial (including aortic) aneurysms, dissections, and rupture.

7 DRUG INTERACTIONS

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

Concomitant Medications

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

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

LAB-0561-5.6

PATIENT INFORMATION

INLYTA® (in-ly-ta)
(axitinib)
tablets

Important information: If your healthcare provider prescribes INLYTA for you to be taken with avelumab or pembrolizumab, also read the Medication Guide for avelumab or pembrolizumab.

What is INLYTA?

INLYTA is a prescription medicine used to treat kidney cancer that has spread or cannot be removed by surgery (advanced renal cell carcinoma or RCC):

- in combination with avelumab or pembrolizumab as your first treatment.
- alone when 1 prior drug treatment regimen for your RCC has not worked.

It is not known if INLYTA is safe and effective in children.

Before taking INLYTA, tell your healthcare provider about all of your medical conditions, including 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 problems, including heart failure
- have an unhealed wound
- plan to have surgery or have had a recent surgery. You should stop taking INLYTA for at least 2 days before planned surgery. See **"What are the possible side effects of INLYTA?"**

For females, tell your healthcare provider if you:

- are pregnant or plan to become pregnant. Taking INLYTA during pregnancy can harm your unborn baby. You should not become pregnant during treatment with INLYTA.
- are able to become pregnant. You should have a pregnancy test before you start treatment with INLYTA. Use effective birth control during treatment and for 1 week after your last dose of INLYTA. Talk to your healthcare provider about birth control methods that you can use to prevent pregnancy during this time.
- are breastfeeding or plan to breastfeed. It is not known if INLYTA passes into your breast milk. Do not breastfeed during treatment and for 2 weeks after your last dose of INLYTA.

For males with female partners who are able to become pregnant:

- Use effective birth control during treatment and for 1 week after your last dose of INLYTA.
- If your female partner becomes pregnant during your treatment with INLYTA, tell your healthcare provider right away.

Tell your healthcare provider 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.

Talk with your healthcare provider before you start taking any new medicine. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take INLYTA?

- Take INLYTA exactly as prescribed by your healthcare provider.
- Your healthcare provider may change your dose if needed.
- INLYTA can be taken with or without food.
- Take INLYTA 2 times a day about 12 hours apart.
- Swallow INLYTA tablets whole with a glass of water.
- Your healthcare provider should check your blood pressure regularly during treatment with INLYTA.
- If you vomit or miss a dose of INLYTA, take your next dose at your regular time. Do not take two doses at the same time.
- If you take too much INLYTA, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking INLYTA?

- Do not drink grapefruit juice or eat grapefruit. Grapefruit may increase the amount of INLYTA in your blood.

What are the possible side effects of INLYTA?

INLYTA may cause serious side effects, including:

- **High blood pressure (hypertension). High blood pressure is common with INLYTA and may sometimes be severe.** Your healthcare provider should check your blood pressure regularly during treatment with INLYTA. If you develop blood pressure problems, your healthcare provider may prescribe medicine to treat your high blood pressure, lower your dose, or stop your treatment with INLYTA.
- **Blood clots in your veins or arteries.** INLYTA can cause blood clots which can be serious, and sometimes lead to death. Get emergency help and call your healthcare provider if you get any of the following symptoms:
  - chest pain or pressure
  - pain in your arms, back, neck or jaw
  - shortness of breath
  - numbness or weakness on one side of your body
  - trouble talking
  - headache
  - vision changes
- **Bleeding.** INLYTA can cause bleeding which can be serious, and sometimes lead to death. Call your healthcare provider right away or get medical help if you develop any of the following signs or symptoms:
  - unexpected bleeding or bleeding that lasts a long time, such as:
    - unusual bleeding from the gums
    - menstrual bleeding or vaginal bleeding that is heavier than normal
    - bleeding that is severe or you cannot control
    - pink or brown urine
    - red or black stools (looks like tar)
    - bruises that happen without a known cause or get larger
    - cough up blood or blood clots
    - vomit blood or your vomit looks like “coffee grounds”
  - unexpected pain, swelling, or joint pain
  - headaches, feeling dizzy or weak
- **Heart failure.** Your healthcare provider should check you for signs or symptoms of heart failure regularly during treatment with INLYTA. Heart failure can be serious and can sometimes lead to death. Tell your healthcare provider if you have any of the following symptoms during your treatment with INLYTA:
  - tiredness
  - swelling of your stomach-area (abdomen), legs or ankles
  - shortness of breath
  - protruding neck veins
- **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-area (abdominal) pain or stomach-area pain that does not go away
  - vomit blood
  - red or black stools
- **Thyroid gland problems.** Your healthcare provider should do blood tests to check your thyroid gland function before and during your treatment with INLYTA. Tell your healthcare provider if you have any of the following symptoms during your treatment with INLYTA:
  - tiredness that worsens or that does not go away
  - feeling hot or cold
  - your voice deepens
  - weight gain or weight loss
  - hair loss
  - muscle cramps and aches
- **Risk of wound healing problems.** Wounds may not heal properly during INLYTA treatment. Tell your healthcare provider if you plan to have any surgery before starting or during treatment with INLYTA.
  - You should stop taking INLYTA at least 2 days before planned surgery.
  - Your healthcare provider should tell you when you may start taking INLYTA again after surgery.

- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** A condition called reversible posterior leukoencephalopathy syndrome (RPLS) can happen during treatment with INLYTA. Call your healthcare provider right away if you get:
  - o headache
  - o seizures
  - o weakness
  - o confusion
  - o high blood pressure
  - o blindness or change in vision
  - o problems thinking
- **Protein in your urine.** Your healthcare provider should check your urine for protein before and during your treatment with INLYTA. If you develop protein in your urine, your healthcare provider may decrease your dose of INLYTA or stop your treatment.
- **Liver problems.** Your healthcare provider will do blood tests before and during your treatment with INLYTA. Your healthcare provider may delay or stop your treatment with INLYTA if you develop severe liver problems.
- **Heart problems.** When INLYTA is used with the medicine avelumab, severe heart problems can happen and can lead to death. Your healthcare provider will check you for heart problems during your treatment with INLYTA. Tell your healthcare provider right away or get medical help if you have any of the following symptoms:
  - o swelling of your stomach-area, legs, hands feet or ankles
  - o shortness of breath
  - o nausea or vomiting
  - o chest discomfort, including pain or pressure
  - o weight gain
  - o pain or discomfort in your arms, back, neck, or jaw
  - o breaking out in a cold sweat
  - o feeling lightheaded or dizzy

The most common side effects of INLYTA with avelumab include:

- o diarrhea
- o feeling tired
- o muscle and bone pain
- o nausea
- o mouth sores
- o rash, redness, itching, or peeling of your skin on your hands and feet
- o hoarseness
- o decreased appetite
- o low levels of thyroid hormone
- o rash
- o liver problems
- o cough
- o shortness of breath
- o stomach-area (abdomen) pain
- o headache

The most common side effects of INLYTA with pembrolizumab include:

- o diarrhea
- o feeling tired or weak
- o liver problems
- o low levels of thyroid hormone
- o decreased appetite
- o rash, redness, itching or peeling of your skin on your hands and feet
- o nausea
- o mouth sores or swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina
- o hoarseness
- o rash
- o cough
- o constipation

The most common side effects of INLYTA when used alone include:

- o diarrhea
- o feeling tired or weak
- o decreased appetite
- o nausea
- o hoarseness
- o rash, redness, itching or peeling of your skin on your hands and feet
- o decreased weight
- o vomiting
- o constipation

INLYTA may cause fertility problems in males and females, which may affect your ability to have a child. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of INLYTA.

Call your healthcare provider 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).

General information about the safe and effective use of 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. You can ask your healthcare provider or pharmacist for information about INLYTA that is written for health professionals.

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.

Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

LAB-0439-5.4

For more information, go to www.inlyta.com or call 8770744-5675
This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: June 2020