

INLYTA- axitinib tablet, film coated
Pfizer Laboratories Div Pfizer Inc

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-----

Warnings and Precautions, Pregnancy (5.13)

8/2018

INDICATIONS AND USAGE-----

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

DOSAGE AND ADMINISTRATION-----

- The starting dose is 5 mg orally twice daily. Dose adjustments can be made based on individual safety and tolerability. (2.1, 2.2)
- Administer INLYTA dose approximately 12 hours apart with or without food. (2.1)
- INLYTA should be swallowed whole with a glass of water. (2.1)
- If a strong CYP3A4/5 inhibitor is required, decrease the INLYTA dose by approximately half. (2.2)
- 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 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 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)
- 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 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, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. (5.6)
- Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment with INLYTA. (5.7)
- Stop INLYTA at least 24 hours prior to scheduled surgery. (5.8)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. Permanently discontinue INLYTA if signs or symptoms of RPLS occur. (5.9)
- 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)
- Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST and bilirubin before initiation of, and periodically throughout, treatment with INLYTA. (5.11)
- The starting dose of INLYTA should be decreased if used in patients with moderate hepatic impairment. INLYTA has not been studied in patients with severe hepatic impairment. (2.2, 5.12)
- INLYTA can cause fetal harm. Advise patients of the potential risk to the fetus and to use effective contraception. (5.13, 8.1, 8.3)

ADVERSE REACTIONS-----

The most common ($\geq 20\%$) adverse reactions are 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)
- Females and males of reproductive potential: May impair fertility. Counsel patients on pregnancy planning and prevention. (8.3)

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

Revised: 8/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INLYTA 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

The recommended starting oral dose of INLYTA is 5 mg twice daily. Administer INLYTA doses approximately 12 hours apart with or without food [see *Clinical Pharmacology (12.3)*]. INLYTA should be swallowed whole with a glass of water.

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.

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)*].

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 antihypertensive therapy. Discontinuation of INLYTA treatment due to hypertension occurred in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib [see *Adverse Reactions (6.1)*].

Blood pressure should be well-controlled prior to initiating INLYTA. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensive medications, reduce the INLYTA dose. Discontinue INLYTA if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis. If INLYTA is interrupted, patients receiving antihypertensive 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 Wound Healing Complications

No formal studies of the effect of INLYTA on wound healing have been conducted.

Stop treatment with INLYTA at least 24 hours prior to scheduled surgery. The decision to resume INLYTA therapy after surgery should be based on clinical judgment of adequate wound healing.

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 Elevation of Liver Enzymes

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 and 2% of patients on the sorafenib arm.

Monitor ALT, aspartate aminotransferase (AST) and bilirubin before initiation of and periodically throughout treatment with INLYTA.

5.12 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 Pregnancy

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)*].

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of INLYTA has been evaluated in 715 patients in monotherapy studies, which included 537 patients with advanced RCC. The data described [see *Adverse Reactions (6.1)*] reflect exposure to INLYTA in 359 patients with advanced RCC who participated in a randomized clinical study versus sorafenib [see *Clinical Studies (14)*].

The following risks, including appropriate action to be taken, are discussed in greater detail in other sections of the label [see *Warnings and Precautions (5)*]: hypertension, arterial thromboembolic events, venous thromboembolic events, hemorrhage, cardiac failure, gastrointestinal perforation and fistula formation, thyroid dysfunction, wound healing complications, RPLS, proteinuria, elevation of liver enzymes, hepatic impairment and fetal development.

6.1 Clinical Trials Experience

The median duration of treatment was 6.4 months (range 0.03 to 22.0) for patients who received INLYTA and 5.0 months (range 0.03 to 20.1) for patients who received sorafenib. Dose modifications or temporary delay of treatment due to an adverse reaction occurred in 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 ($\geq 20\%$) adverse reactions observed following treatment with INLYTA were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation. Table 1 presents adverse reactions reported in $\geq 10\%$ patients who received INLYTA or sorafenib.

Table 1. Adverse Reactions Occurring in $\geq 10\%$ of Patients Who Received INLYTA or Sorafenib

Adverse Reaction *	INLYTA		Sorafenib	
	(N=359)		(N=355)	
	All Grades [†]	Grade 3/4	All Grades [†]	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

* Percentages are treatment-emergent, all-causality events

† 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 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

Laboratory Abnormality	N	INLYTA		N	Sorafenib	
		All Grades *	Grade 3/4		All Grades *	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

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase

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

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).

7 DRUG INTERACTIONS

In vitro data indicate that axitinib is metabolized primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

7.1 CYP3A4/5 Inhibitors

Co-administration of ketoconazole, a strong inhibitor of CYP3A4/5, increased the plasma exposure of axitinib in healthy volunteers. Co-administration of INLYTA with strong CYP3A4/5 inhibitors should be avoided. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, the INLYTA dose should be reduced [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

7.2 CYP3A4/5 Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies and its mechanism of action, 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, axitinib was teratogenic, embryotoxic and fetotoxic in mice at exposures lower than human exposures at the recommended starting dose (*see Data*). Advise females of reproductive potential of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated populations are unknown. However, the background risk in the United States (U.S.) general population of major birth defects is 2%–4% and of miscarriage is 15%–20% of clinically recognized pregnancies.

Data

Animal Data

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

8.2 Lactation

Risk Summary

There are no data on the presence of axitinib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child from INLYTA, advise lactating women not to breastfeed during treatment and for 2 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on findings in animal studies, INLYTA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Females of reproductive potential should have a pregnancy test prior to starting treatment with INLYTA.

Contraception

Females

INLYTA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with INLYTA and for 1 week after the last dose.

Males

Based on findings in animal studies, advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose.

Infertility

Females and Males

Based on findings in animals, INLYTA may impair fertility in females and males of reproductive potential [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

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

Toxicities in bone and teeth were observed in immature mice and dogs administered oral axitinib twice daily for 1 month or longer. Effects in bone consisted of thickened growth plates in mice and dogs at

≥15 mg/kg/dose (approximately 6 and 15 times, respectively, the systemic exposure (AUC) in patients at the recommended starting dose). Abnormalities in growing incisor teeth (including dental caries, malocclusions and broken and/or missing teeth) were observed in mice administered oral axitinib twice daily at ≥5 mg/kg/dose (approximately 1.5 times the AUC in patients at the recommended starting dose). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

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

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

8.7 Renal Impairment

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

10 OVERDOSAGE

There is no specific treatment for INLYTA overdose.

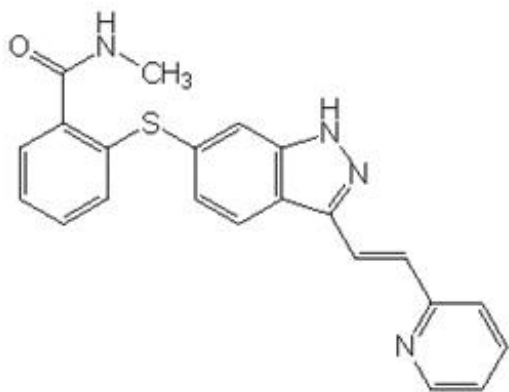
In a controlled clinical study with INLYTA for the treatment of patients with RCC, 1 patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with INLYTA, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal hemoptysis.

In cases of suspected overdose, INLYTA should be withheld and supportive care instituted.

11 DESCRIPTION

INLYTA (axitinib) is a kinase inhibitor. Axitinib has the chemical name N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide. The molecular formula is C₂₂H₁₈N₄OS and the molecular weight is 386.47 Daltons. The chemical structure is:



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

INLYTA is supplied as red, film-coated tablets containing either 1 mg or 5 mg of axitinib together with microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry® II red 32K15441 as inactive ingredients. The Opadry II red 32K15441 film coating contains lactose monohydrate, HPMC 2910/Hypromellose 15cP, titanium dioxide, triacetin (glycerol triacetate), and red iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

Absorption and Distribution: Following single oral 5-mg dose administration, the median T_{max} ranged from 2.5 to 4.1 hours. Based on the plasma half-life, steady state is expected within 2 to 3 days of dosing. Dosing of axitinib at 5 mg twice daily resulted in approximately 1.4-fold accumulation compared to administration of a single dose. At steady state, axitinib exhibits approximately linear pharmacokinetics within the 1-mg to 20-mg dose range. The mean absolute bioavailability of axitinib after an oral 5 mg dose is 58%.

Compared to overnight fasting, administration of INLYTA with a moderate fat meal resulted in 10% lower AUC and a high fat, high-calorie meal resulted in 19% higher AUC. INLYTA can be

administered with or without food [see Dosage and Administration (2.1)].

Axitinib is highly bound (>99%) to human plasma proteins with preferential binding to albumin and moderate binding to α_1 -acid glycoprotein. In patients with advanced RCC (n=20), at the 5 mg twice daily dose in the fed state, the geometric mean (CV%) C_{max} and AUC_{0-24} were 27.8 (79%) ng/mL and 265 (77%) ng.h/mL, respectively. The geometric mean (CV%) clearance and apparent volume of distribution were 38 (80%) L/h and 160 (105%) L, respectively.

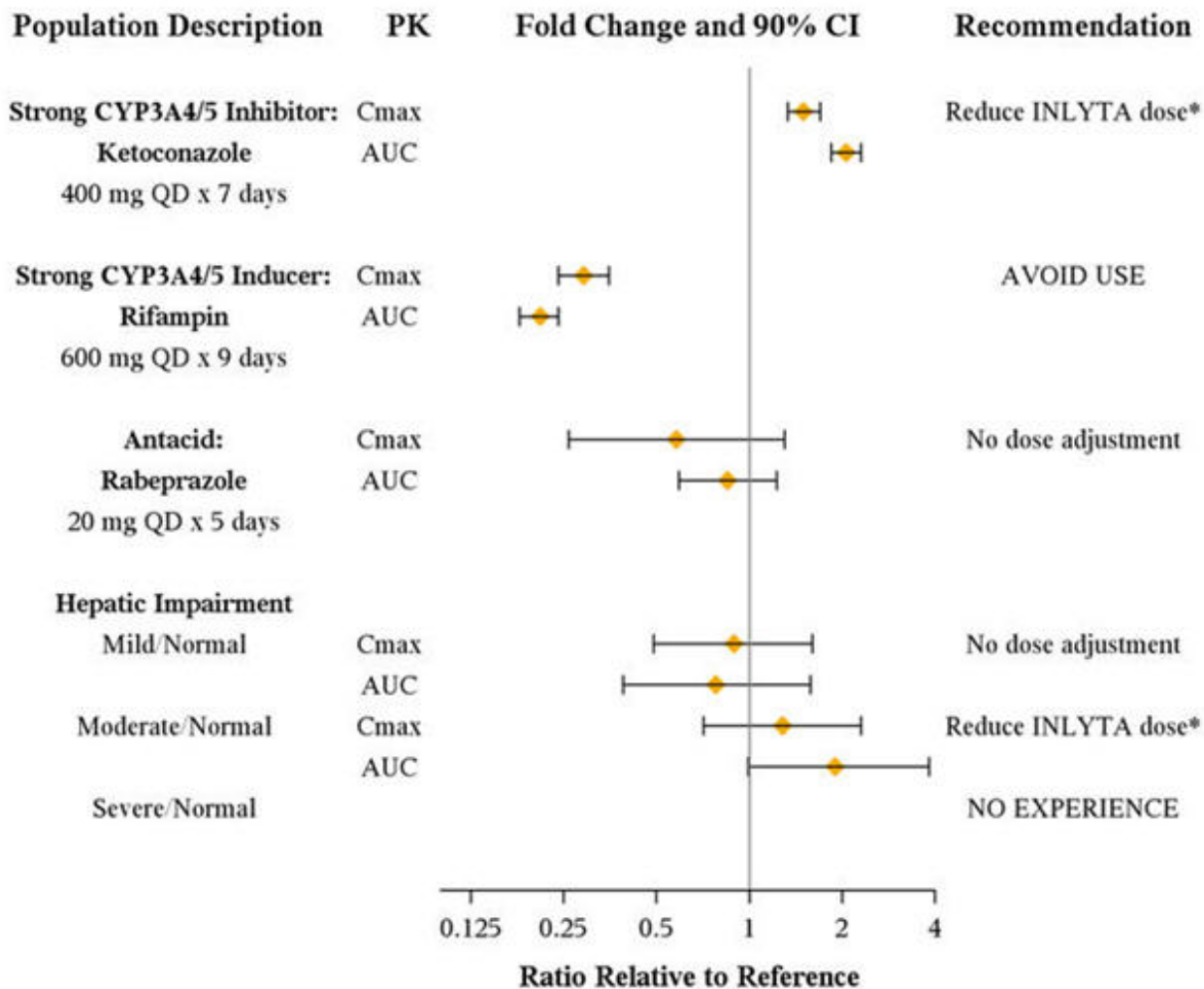
Metabolism and Elimination: The plasma half-life of INLYTA ranges from 2.5 to 6.1 hours. Axitinib is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. Following oral administration of a 5-mg radioactive dose of axitinib, approximately 41% of the radioactivity was recovered in feces and approximately 23% was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in feces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity.

The sulfoxide and N-glucuronide metabolites show approximately ≥ 400 -fold less in vitro potency against VEGFR-2 compared to axitinib.

Drug-Drug Interactions

Effects of Other Drugs on INLYTA: Axitinib is metabolized primarily in the liver by CYP3A4/5. Additionally, the aqueous solubility of axitinib is pH dependent, with higher pH resulting in lower solubility. The effects of a strong CYP3A4/5 inhibitor, a strong CYP3A4/5 inducer, and an antacid on the pharmacokinetics of axitinib are presented in Figure 1 [see Dosage and Administration (2.2) and Drug Interactions (7.1, 7.2)].

Figure 1. Impact of Co-administered Drugs and Hepatic Impairment on Axitinib Pharmacokinetics



AUC: area under the curve; C_{max}: maximum concentration. *See Dosage and Administration (2).

Effects of INLYTA on Other Drugs: In vitro studies demonstrated that axitinib has the potential to inhibit CYP1A2 and CYP2C8. However, co-administration of axitinib with paclitaxel, a CYP2C8 substrate, did not increase plasma concentrations of paclitaxel in patients.

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 in human hepatocytes indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5.

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

Pharmacokinetics in Specific Populations

Pediatric Use: INLYTA has not been studied in patients <18 years of age.

Hepatic Impairment: The effects of hepatic impairment on the pharmacokinetics of axitinib are presented in Figure 1 [see Dosage and Administration (2.2), Warnings and Precautions (5.12), Use in Specific Populations (8.6)].

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 ≤ CL_{cr} < 29 mL/min), 64 with moderate renal impairment (30 mL/min ≤ CL_{cr} < 59 mL/min), and 139 with mild renal impairment (60 mL/min ≤ CL_{cr} < 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 [see Use in Specific Populations (8.7)].

Other Intrinsic Factors: Population pharmacokinetic analyses indicate that there are no clinically relevant effects of age, gender, race, body weight, body surface area, UGT1A1 genotype, or CYP2C19 genotype on the clearance of axitinib.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with axitinib.

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

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

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

14 CLINICAL STUDIES

The safety and efficacy of INLYTA were evaluated in a randomized, open-label, multicenter Phase 3 study. Patients (N=723) with advanced RCC whose disease had progressed on or after treatment with 1 prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomized (1:1) to receive INLYTA (N=361) or sorafenib (N=362). Progression-free survival (PFS) was assessed by a blinded independent central review committee. Other endpoints included objective response rate (ORR) and overall survival (OS).

Of the patients enrolled in this study, 389 patients (54%) had received 1 prior sunitinib-based therapy, 251 patients (35%) had received 1 prior cytokine-based therapy (interleukin-2 or interferon-alfa), 59 patients (8%) had received 1 prior bevacizumab-based therapy, and 24 patients (3%) had received 1 prior temsirolimus-based therapy. The baseline demographic and disease characteristics were similar between the INLYTA and sorafenib groups with regard to age (median 61 years), gender (72% male), race (75% white, 21% Asian), Eastern Cooperative Oncology Group (ECOG) performance status (55% 0, 45% 1), and histology (99% clear cell).

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

Table 3. Efficacy Results

Endpoint/Study Population	INLYTA	Sorafenib	HR (95% CI)	P-value
Overall ITT	N= 361	N = 362		

Median PFS ^{*,†} in months (95% CI)	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)	0.67 (0.54, 0.81)	<0.0001 [‡]
Median OS in months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	NS
ORR % (95% CI)	19.4 (15.4, 23.9)	9.4 (6.6, 12.9)	2.06 [§] (1.41, 3.00)	-¶
PFS by prior treatment				
Sunitinib-refractory subgroup	N=194	N=195		
Median, months (95% CI)	4.8 (4.5, 6.4)	3.4 (2.8, 4.7)	0.74 (0.57, 0.96)	-¶
Cytokine-refractory subgroup	N=126	N=125		
Median, months (95% CI)	12.1 (10.1, 13.9)	6.5 (6.3, 8.3)	0.46 (0.32, 0.68)	-¶

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

* Time from randomization to progression or death due to any cause, whichever occurs first.

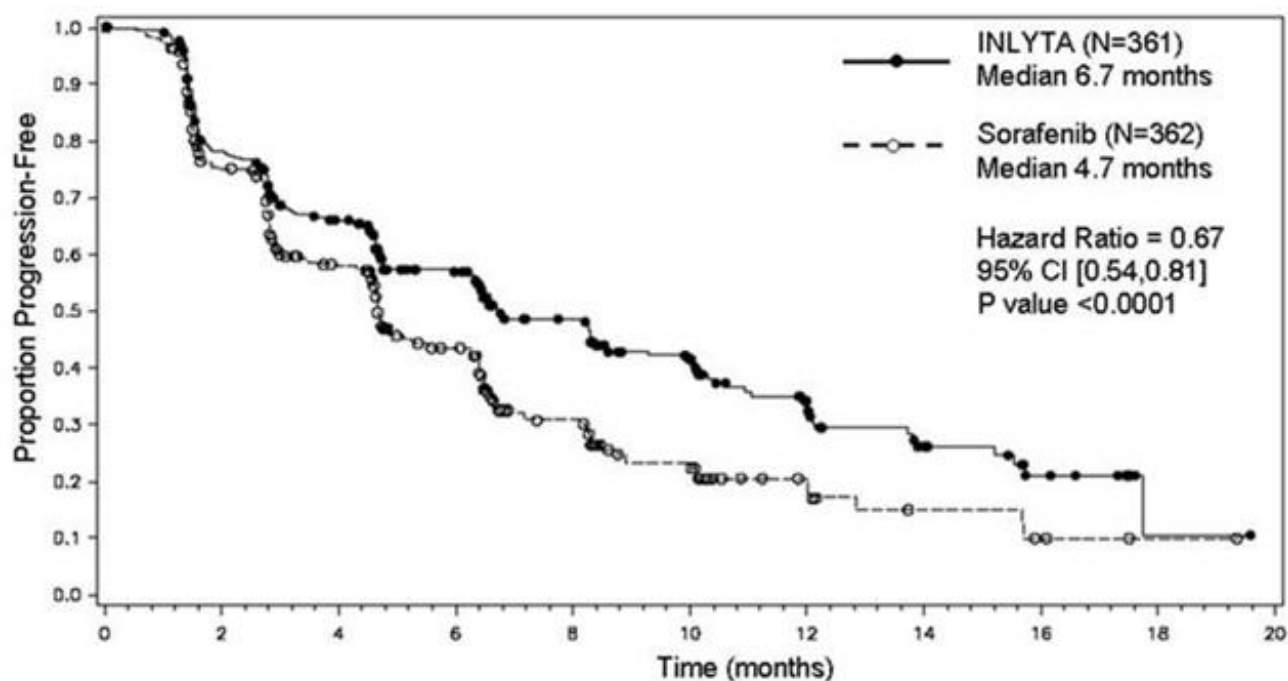
† Assessed by independent radiology review according to RECIST.

‡ One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy (comparison is considered statistically significant if the one-sided p-value is <0.023).

§ Risk ratio is used for ORR. A risk ratio >1 indicated a higher likelihood of responding in the axitinib arm; a risk ratio <1 indicated a higher likelihood of responding in the sorafenib arm.

¶ P-value not included since it was not adjusted for multiple testing.

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



16 HOW SUPPLIED/STORAGE AND HANDLING

INLYTA tablets are supplied as follows:

- 1 mg tablets are red film-coated, oval tablets debossed with "Pfizer" on one side and "1 XNB" on the other; available in bottles of 180: NDC 0069-0145-01.
- 5 mg tablets are red film-coated, triangular tablets debossed with "Pfizer" on one side and "5 XNB" on the other; available in bottles of 60: NDC 0069-0151-11.
- Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypertension

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

Arterial/Venous Thromboembolic Events

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

Hemorrhage

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

Cardiac Failure

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

Gastrointestinal Disorders

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

Abnormal Thyroid Function

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

Wound Healing Complications

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

Reversible Posterior Leukoencephalopathy Syndrome

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

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with INLYTA and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week following the last dose [see *Warnings and Precautions (5.13)* and *Use in Specific Populations (8.3)*].

Lactation

Advise patients not to breastfeed while taking INLYTA and for 2 weeks after receiving the last dose [see *Use in Specific Populations (8.2)*].

Concomitant Medications

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

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



LAB- 0561-4.0

PATIENT INFORMATION

INLYTA[®] (in-ly-ta)
(axitinib)
tablets

What is INLYTA?

INLYTA is a prescription medicine used to treat advanced kidney cancer (advanced renal cell carcinoma or RCC) 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 failure
- have an unhealed wound
- plan to have surgery. You should stop taking INLYTA at least 24 hours before planned surgery.
- have any other medical conditions

For females, tell your 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 while taking INLYTA. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- 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 at least 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 at least 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 at least 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.
- **Problem with 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
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** A condition called reversible posterior leukoencephalopathy syndrome (RPLS) can happen while taking INLYTA. Call your healthcare provider right away if you get:
 - headache
 - seizures
 - weakness
 - confusion
 - high blood pressure
 - blindness or change in vision
 - 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.
- **Change in liver function.** Your healthcare provider should do blood tests before and during your treatment with INLYTA to check your liver function.

The most common side effects of INLYTA include:

- diarrhea (frequent or loose bowel movements)
- tiredness or feeling weak
- decreased appetite
- nausea
- hoarseness
- rash, redness, itching or peeling of your skin on your hands and feet
- decreased weight
- vomiting
- 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.



LAB-0439-4.0

For more information, go to www.inlyta.com or call 8770744-5675

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

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: August 2018

PRINCIPAL DISPLAY PANEL - 1 mg Tablet Bottle Label

Pfizer

NDC 0069-0145-01

**Inlyta®
(axitinib) tablets**

1 mg

180 Tablets

Rx only

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

DOSAGE AND USE
See accompanying prescribing information.
Each tablet contains 1 mg of axitinib.
Dispense in tight (USP), child-resistant containers.

Distributed by: Pfizer Labs
Division of Pfizer Inc, NY, NY 10017
MADE IN IRELAND

Pfizer NDC 0069-0145-01

Inlyta[®]
(axitinib) tablets

1 mg

180 Tablets **Rx only**

Exp.
Lot
SN

GTIN:
00300690145013
PAA073114

N3 0069-0145-01 3

PRINCIPAL DISPLAY PANEL - 5 mg Tablet Bottle Label

Pfizer

NDC 0069-0151-11

Inlyta[®]
(axitinib) tablets

5 mg

60 Tablets

Rx only

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

DOSAGE AND USE
See accompanying prescribing information.
Each tablet contains 5 mg of axitinib.
Dispense in tight (USP), child-resistant containers.

Distributed by: Pfizer Labs
Division of Pfizer Inc, NY, NY 10017
MADE IN IRELAND

Pfizer NDC 0069-0151-11

Inlyta[®]
(axitinib) tablets

5 mg

60 Tablets **Rx only**

Exp.
Lot
SN

GTIN:
00300690151113
PAA073115

N3 0069-0151-11 3

INLYTA

axitinib tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0069-0145
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AXITINIB (UNII: C9LVQ0YUXG) (AXITINIB - UNII:C9LVQ0YUXG)	AXITINIB	1 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
HYPROMELLOSE 2910 (15000 MPA.S) (UNII: 288VBX44JC)	

Product Characteristics

Color	RED	Score	no score
Shape	OVAL	Size	9mm
Flavor		Imprint Code	Pfizer;1;XNB
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0069-0145-01	180 in 1 BOTTLE; Type 0: Not a Combination Product	01/27/2012	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202324	01/27/2012	

INLYTA

axitinib tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0069-0151
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AXITINIB (UNII: C9LVQ0YUXG) (AXITINIB - UNII:C9LVQ0YUXG)	AXITINIB	5 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
HYPROMELLOSE 2910 (15000 MPA.S) (UNII: 288VBX44JC)	

Product Characteristics

Color	RED	Score	no score
Shape	TRIANGLE	Size	8mm
Flavor		Imprint Code	Pfizer;5;XNB
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0069-0151-11	60 in 1 BOTTLE; Type 0: Not a Combination Product	01/27/2012	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202324	01/27/2012	

Labeler - Pfizer Laboratories Div Pfizer Inc (134489525)**Establishment**

Name	Address	ID/FEI	Business Operations
Pfizer Ireland Pharmaceuticals		989811526	ANALYSIS(0069-0151, 0069-0145) , API MANUFACTURE(0069-0151, 0069-0145)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Pharmaceuticals LLC		829084552	ANALYSIS(0069-0151, 0069-0145) , PACK(0069-0151, 0069-0145)

Establishment			
Name	Address	ID/FEI	Business Operations
Pfizer Manufacturing Deutschland GmbH (Betriebsstätte Freiburg)		341970073	ANALYSIS(0069-0151, 0069-0145) , LABEL(0069-0151, 0069-0145) , MANUFACTURE(0069-0151, 0069-0145) , PACK(0069-0151, 0069-0145)

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Pfizer Laboratories Div Pfizer Inc