HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AXITINIB TABLETS safely and effectively. See full prescribing information for AXITINIB TABLETS.
AXITINIB tablets, for oral administration
Initial U.S. Approval: 2012

---------- INDICATIONS AND USAGE----------
Axitinib tablets are a kinase inhibitor indicated:
- 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 ----------
- Axitinib tablets 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 axitinib tablets dose approximately 12 hours apart with or without food. (2.1)
- Axitinib tablets should be swallowed whole with a glass of water. (2.1)
- See Full Prescribing Information for dosage modifications for adverse reactions. (2.2)
- If a strong CYP3A4/5 inhibitor is required, decrease the axitinib tablets 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: Hypertension including hypertensive crisis has been observed. Blood pressure should be well-controlled prior to initiating axitinib tablets. Monitor for hypertension and treat as needed. Withhold and then dose reduce axitinib tablets or permanently discontinue based on severity of hypertension. (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. Permanently discontinue axitinib tablets if an arterial thromboembolic event occurs during treatment. Withhold axitinib tablets and then resume at same dose or permanently discontinue based on severity of VTE. (5.2, 5.3)
- Hemorrhage: Hemorrhagic events, including fatal events, have been reported. Axitinib tablets have not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. Withhold and then dose reduce axitinib tablets or discontinue based on severity and persistence of hemorrhage. (5.4)
- Cardiac Failure: Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with axitinib tablets. Management of cardiac failure may require dose reduction, dose interruption or permanent discontinuation of axitinib tablets. (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 axitinib tablets. (5.7)
- Impaired Wound Healing: Withhold axitinib tablets 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. Resume axitinib tablets at a reduced dose or discontinue based on severity and persistence of the impaired wound healing. The safety of resumption of axitinib tablets after resolution of wound healing complications has not been established. (5.8)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS has been observed. Permanently discontinue axitinib tablets if signs or symptoms of RPLS occur. (5.9)
- Proteinuria: Monitor for proteinuria before initiation of, and periodically throughout, treatment with axitinib tablets. For moderate to severe proteinuria, withhold and then dose reduce axitinib tablets. (5.10)
- Hepatotoxicity: Liver enzyme elevation has occurred during treatment with axitinib tablets as a single agent. Monitor ALT, AST and bilirubin before initiation of, and periodically throughout, treatment with axitinib tablets. (5.11)
- Use in Patients with Hepatic Impairment: Decrease the starting dose of axitinib tablets if used in patients with moderate hepatic impairment. Axitinib tablets have not been studied in patients with severe hepatic impairment. (2.2, 5.12)
- Embryo-Fetal Toxicity: Axitinib tablets 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:

Axitinib tablets 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 Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

---------- DRUG INTERACTIONS----------
- Avoid strong CYP3A4/5 inhibitors. If unavoidable, reduce the axitinib tablets 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: 2/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.2 Second-Line Advanced Renal Cell Carcinoma

Axitinib tablets as a single agent is indicated for the treatment of advanced RCC after failure of one prior systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Second-Line Advanced RCC

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

Important Administration Instructions

Advise patients to swallow axitinib tablets 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. Recommended axitinib tablets dosage increases and reductions are provided in Table 1.

Over the course of treatment, patients who tolerate axitinib tablets 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.

Table 1: Recommended Dosage Increases and Reductions for Axitinib Tablets

Dose Modification	**Dose Regimen**
Recommended starting dosage	5 mg twice daily
Dosage increase	
First dose increase	7 mg twice daily
Second dose increase	10 mg twice daily
Dosage reduction[a]	
First dose reduction[b]	3 mg twice daily
Second dose reduction	2 mg twice daily

[a]: for management of adverse drug reactions
[b]: from 5 mg twice daily

Recommended dosage modifications for adverse reactions for axitinib tablets are provided in Table 2.

Table 2: Recommended Dosage Modification for Axitinib Tablets for Adverse Reactions

Adverse Reaction	Severity	Dosage Modifications for Axitinib Tablets
Hypertension [*see Warnings and Precautions (5.1)*]	SBP > 150 mmHg or DBP > 100 mmHg despite antihypertensive treatment	• Reduce dose by one level.
	SBP > 160 mmHg or DBP > 105 mmHg	• Withhold until BP < 150/100 mmHg. • Resume at a reduced dose.
	Grade 4 or hypertensive crisis	• Permanently discontinue.
Hemorrhage [*see Warnings and Precautions (5.4)*]	Grade 3 or 4	• Withhold until resolution to Grade 0 or 1 or baseline. • Either resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
Cardiac failure [*see Warnings and Precautions (5.5)*]	Asymptomatic cardiomyopathy (left ventricular ejection fraction greater than 20% but less than 50% below baseline or below the lower limit of normal if baseline was not obtained)	• Withhold until resolution to Grade 0 or 1 or baseline. • Resume at a reduced dose.
	Clinically manifested congestive heart failure	• Permanently discontinue.
Impaired wound healing [*see Warnings and Precautions (5.8)*]	Any Grade	• The safety of resumption of axitinib tablets after resolution of wound healing has not been established. • Either resume at a reduced dose or discontinue depending on the severity and persistence of the adverse reaction.
Reversible Posterior Leukoencephalopathy Syndrome [*see Warnings and Precautions (5.9)*]	Any Grade	• Permanently discontinue.
Proteinuria [*see Warnings and Precautions (5.10)*]	2 or more grams proteinuria per 24 hours	• Withhold until resolution to less than 2 grams per 24 hours. • Resume at a reduced dose.
Other Adverse Reactions	Grade 3	• Reduce dosage by one level.
	Grade 4	• Withhold until resolution to Grade 2. • Resume at a reduced dose.

2.3 Dosage Modification for Drug Interactions

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 axitinib tablets 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 axitinib tablets 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 axitinib tablets dose should be returned (after 3 to 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)].*

2.4 Dosage Modification for Hepatic Impairment

No starting dose adjustment is required when administering axitinib tablets to patients with mild hepatic impairment (Child-Pugh class A). Based on the pharmacokinetic data, the axitinib tablets 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. Axitinib tablets have 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 axitinib: red, capsule shape, biconvex film-coated tablets. Engraved “APO” on one side, “AX1”on the other side.
- 5 mg tablets of axitinib: red, triangular shape, biconvex film-coated tablets. Engraved “AX” over “5” on one side, “APO” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

In a controlled clinical study with axitinib tablets for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving axitinib tablets and 103/355 patients (29%) receiving sorafenib. Grade 3/4 hypertension was observed in 56/359 patients (16%) receiving axitinib tablets and 39/355 patients (11%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) receiving axitinib tablets 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 axitinib tablets treatment and blood pressure increases have been observed as early as 4 days after starting axitinib tablets. Hypertension was managed with standard anti-hypertensive therapy. Discontinuation of axitinib tablets treatment due to hypertension occurred in 1/359 patients (<1%) receiving axitinib tablets and none of the patients receiving sorafenib *[see Adverse Reactions (6.1)]*.

Ensure that blood pressure is well-controlled prior to initiating axitinib tablets. Monitor patients for hypertension and treat as needed with standard anti-hypertensive therapy. Withhold and then dose reduce axitinib tablets or permanently discontinue based on severity of hypertension *[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 axitinib tablets for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving axitinib tablets and 4/355 patients (1%) receiving sorafenib. Fatal cerebrovascular accident was reported in 1/359 patients (<1%) receiving axitinib tablets and none of the patients receiving sorafenib *[see Adverse Reactions (6.1)]*.

Axitinib tablets have not been studied in patients who had an arterial thromboembolic event within the previous 12 months. In clinical trials with axitinib tablets, 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.

Permanently discontinue axitinib tablets if an arterial thromboembolic event occurs during treatment.

5.3 Venous Thromboembolic Events

In clinical trials, venous thromboembolic events have been reported, including deaths. In a controlled clinical study with axitinib tablets for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving axitinib tablets and 2/355 patients (1%) receiving sorafenib. Grade 3/4 venous thromboembolic events were reported in 9/359 patients (3%) receiving axitinib tablets (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 axitinib tablets and none of the patients receiving sorafenib.

Axitinib tablets have not been studied in patients who had a venous thromboembolic event within the previous 6 months. In clinical trials with axitinib tablets, venous thromboembolic events were reported in 22/715 patients (3%), with two deaths secondary to pulmonary embolism.

Monitor for signs and symptoms of VTE and PE. Withhold axitinib tablets and then resume at same dose or permanently discontinue based on severity of VTE.

5.4 Hemorrhage

In a controlled clinical study with axitinib tablets for the treatment of patients with RCC, hemorrhagic events were reported in 58/359 patients (16%) receiving axitinib tablets and 64/355 patients (18%) receiving sorafenib. Grade 3/4 hemorrhagic events were reported in 5/359 (1%) patients receiving axitinib tablets (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 axitinib tablets (gastric hemorrhage) and 3/355 patients (1%) receiving sorafenib.

Axitinib tablets have 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. Withhold and then dose reduce axitinib tablets or discontinue based on severity and persistence of hemorrhage.

5.5 Cardiac Failure

In a controlled clinical study with axitinib tablets for the treatment of patients with RCC, cardiac failure was reported in 6/359 patients (2%) receiving axitinib tablets and 3/355 patients (1%) receiving sorafenib. Grade 3/4 cardiac failure was observed in 2/359 patients (1%) receiving axitinib tablets and 1/355 patients (<1%) receiving sorafenib. Fatal cardiac failure was reported in 2/359 patients (1%) receiving axitinib tablets and 1/355 patients (<1%) receiving sorafenib. Monitor for signs or symptoms of cardiac failure throughout treatment with axitinib tablets. Management of cardiac failure may require dose reduction, dose interruption or permanent discontinuation of axitinib tablets *[see Dosage and Administration (2.2)]*.

5.6 Gastrointestinal Perforation and Fistula Formation

In a controlled clinical study with axitinib tablets for the treatment of patients with RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving axitinib tablets and none of the patients receiving sorafenib. In clinical trials with axitinib tablets, 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 axitinib tablets.

5.7 Thyroid Dysfunction

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

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

5.8 Impaired Wound Healing

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

Withhold axitinib tablets 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. Resume axitinib tablets at a reduced dose or discontinue based on severity and persistence of the impaired wound healing. The safety of resumption of axitinib tablets after resolution of wound healing complications has not been established *[see Dosage and Administration (2.2)]*.

5.9 Reversible Posterior Leukoencephalopathy Syndrome

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

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. Permanently discontinue axitinib tablets in patients developing RPLS. The safety of reinitiating axitinib tablets therapy in patients previously experiencing RPLS is not known *[see Dosage and Administration (2.2)]*.

5.10 Proteinuria

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

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib tablets is recommended. For patients who develop moderate to severe proteinuria, withhold and then dose reduce axitinib tablets *[see Dosage and Administration (2.2)]*.

5.11 Hepatotoxicity

Axitinib Tablets as a Single Agent

In a controlled clinical study with axitinib tablets 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 axitinib tablets arm. When used as a single agent, monitor ALT, aspartate aminotransferase (AST) and bilirubin before initiation of and periodically throughout treatment with axitinib tablets.

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 axitinib tablets to patients with moderate hepatic impairment (Child-Pugh class B). Axitinib tablets have 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)]*.

5.14 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, axitinib tablets 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 axitinib tablets and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with axitinib tablets and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

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

- Hypertension *[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 axitinib tablets 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 axitinib tablets in 359 patients with advanced RCC who participated in a randomized clinical study versus sorafenib *[see Clinical Studies (14.2)]*.

Second-Line Advanced RCC

The median duration of treatment was 6.4 months (range 0.03 to 22) for patients who received axitinib tablets and 5 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 axitinib tablets and 220/355 patients (62%) receiving sorafenib. Permanent discontinuation due to an adverse reaction occurred in 34/359 patients (9%) receiving axitinib tablets and 46/355 patients (13%) receiving sorafenib.

The most common (≥20%) adverse reactions observed following treatment with axitinib tablets were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation. Table 8 presents adverse reactions reported in ≥10% patients who received axitinib tablets or sorafenib.

Table 8: Adverse Reactions Occurring in ≥10% of Patients Who Received Axitinib Tablets or Sorafenib

Adverse Reaction[a]	Axitinib (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 axitinib tablets 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 9 presents the most common laboratory abnormalities reported in ≥10% patients who received axitinib tablets or sorafenib.

Table 9: Laboratory Abnormalities Occurring in ≥10% of Patients Who Received Axitinib Tablets or Sorafenib

Laboratory Abnormality	N	Axitinib		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 axitinib tablets included hemoglobin increased (above the upper limit of normal) (9% for axitinib tablets versus 1% for sorafenib) and hypercalcemia (6% for axitinib tablets versus 2% for sorafenib).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of axitinib tablets. 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 axitinib tablets 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 axitinib tablets 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 axitinib tablets with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentine, 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, axitinib tablets 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% to 4% and of miscarriage is 15% to 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 axitinib tablets, advise lactating women not to breastfeed during treatment and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Based on findings in animal studies, axitinib tablets can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating treatment with axitinib tablets.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with axitinib tablets 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, axitinib tablets may impair fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

The safety and effectiveness of axitinib tablets in pediatric patients have not been established.

The safety and effectiveness of axitinib tablets were assessed, but not established, in two open label studies: a dose finding study of axitinib tablets as a single agent in 17 pediatric patients aged 5 to <17 years with recurrent or refractory solid tumors (ADVL1315, NCT02164838) and a randomized study of axitinib tablets as a single agent or in combination in 7 pediatric patients aged 7 to <17 years (AREN1721, NCT03595124).

No new safety signals were observed with axitinib tablets in pediatric patients across these studies.

Exposure in pediatric patients who received axitinib tablets at the maximum tolerated dosage were lower than those previously observed in adults who received the approved recommended starting dosage.

Juvenile Animal Toxicity Data

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 axitinib tablets for the treatment of patients with RCC, 123/359 patients (34%) treated with axitinib tablets 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 axitinib tablets 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 axitinib tablets 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 axitinib tablets to patients with mild hepatic impairment (Child-Pugh class A). A starting dose decrease is recommended when administering axitinib tablets 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)]*.

Axitinib tablets have not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

8.7 Renal Impairment

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

10 OVERDOSAGE

There is no specific treatment for axitinib tablets overdose.

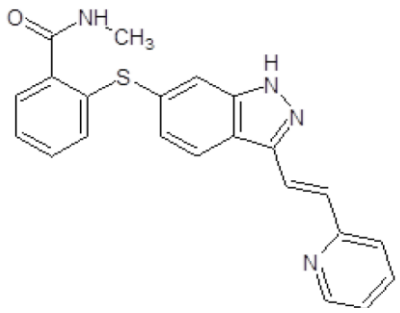
In a controlled clinical study with axitinib tablets for the treatment of patients with RCC, 1 patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with axitinib tablets, 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, axitinib tablets should be withheld and supportive care instituted.

11 DESCRIPTION

Axitinib tablets (axitinib) is a kinase inhibitor. Axitinib has the chemical name Benzamide, *N*-methyl-2-[[3-[(1*E*)-2-(2-pyridinyl)ethenyl]-1*H*-indazol-6-yl]thio]-. The molecular formula is $C_{22}H_{18}N_4OS$ and the molecular weight is 386.47. 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 mcg/mL. The partition coefficient (n-octanol/water) is 3.5.

Axitinib tablets are supplied as red, film-coated tablets containing either 1 mg or 5 mg of axitinib together with croscarmellose sodium, ethyl cellulose, magnesium stearate, and microcrystalline cellulose. The film coating contains hypromellose, iron oxide red, titanium dioxide, and triacetin.

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 axitinib tablets (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 axitinib tablets with a moderate fat meal resulted in 10% lower AUC and a high fat, high-calorie meal resulted in 19% higher AUC. Axitinib tablets 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 α1-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 axitinib tablets 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.

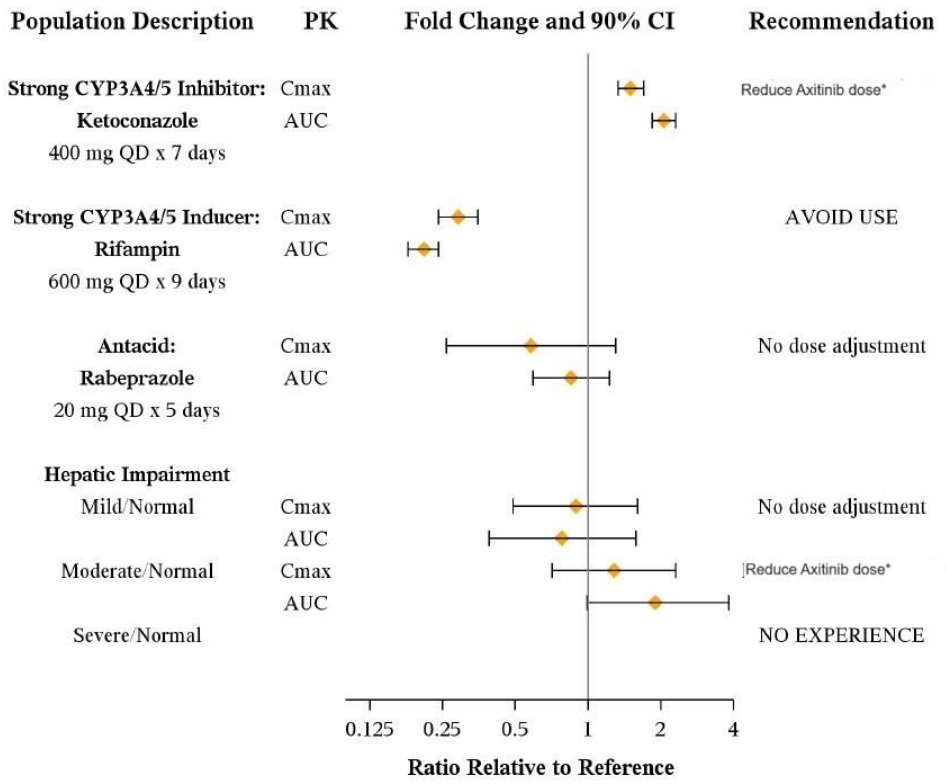
The sulfoxide and N-glucuronide metabolites show approximately ≥400-fold less *in vitro* potency against VEGFR-2 compared to axitinib.

Drug-Drug Interactions

Effects of Other Drugs on Axitinib Tablets

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; Cmax: maximum concentration. *See Dosage and Administration (2).

Effects of Axitinib Tablets 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, axitinib tablets are not expected to inhibit P-gp at therapeutic plasma concentrations.

Specific Populations

Patients with 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)]*.

Patients with Renal Impairment

Population pharmacokinetic analysis (based on pre-existing renal function) was carried out in 590 healthy volunteers and patients, including five with severe renal impairment (15 mL/min ≤CLcr <29 mL/min), 64 with moderate renal impairment (30 mL/min ≤CLcr <59 mL/min), and 139 with mild renal impairment (60 mL/min ≤CLcr <89 mL/min). Mild to severe renal impairment did not have meaningful effects on the pharmacokinetics of axitinib. Data from only

one patient with end-stage renal disease are available *[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.

Axitinib tablets have 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

14.2 Second-Line Advanced RCC

The safety and efficacy of axitinib tablets 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 axitinib tablets (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 axitinib tablets 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 axitinib tablets over sorafenib for the endpoint of PFS (see Table

12 and Figure 4). There was no statistically significant difference between the arms in OS.

Table 12: Efficacy Results

Endpoint/Study Population	Axitinib	Sorafenib	HR (95% CI)	P-value
Overall ITT	N= 361	N = 362		
Median PFS[a,b] in months (95% CI)	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)	0.67 (0.54, 0.81)	<0.0001[c]
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[d] (1.41, 3.00)	_e
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)	_e
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)	_e

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

[a] Time from randomization to progression or death due to any cause, whichever occurs first.

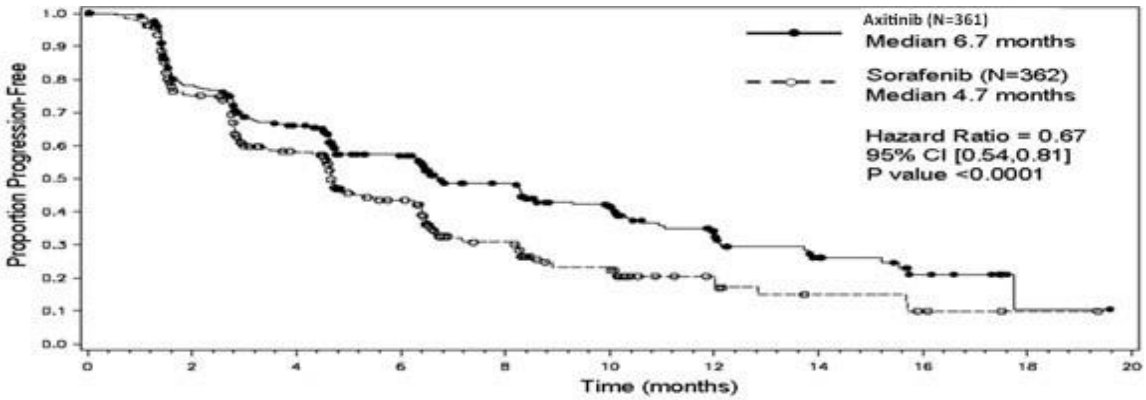
[b] Assessed by independent radiology review according to RECIST.

[c] 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).

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

[e] P-value not included since it was not adjusted for multiple testing.

Figure 4. Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment (Intent-to-Treat Population)



16 HOW SUPPLIED/STORAGE AND HANDLING

Axitinib Tablets are supplied as follows:

- 1 mg tablets are red, capsule shape, biconvex film-coated tablets. Engraved “APO” on one side, “AX1”on the other side.

Bottles of 180: NDC 60505-4427-8.

- 5 mg tablets are red, triangular shape, biconvex film-coated tablets. Engraved “AX” over “5” on one side, “APO”

on the other side.

Bottles of 60: NDC 60505-4428-6.

- 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 axitinib tablets 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 axitinib tablets 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 axitinib tablets 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 axitinib tablets 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 axitinib tablets 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 axitinib tablets *[see Warnings and Precautions (5.6) and Adverse Reactions (6.1)]*.

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

Impaired Wound Healing
Advise patients that axitinib tablets may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure *[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)]*.

Hepatotoxicity
Inform patients of the signs and symptoms of hepatotoxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatotoxicity *[see Warnings and Precautions (5.11)].*

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 axitinib tablets 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 (5.14) and Use in Specific Populations (8.3)]*.

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

Infertility
Advise males and females of reproductive potential that axitinib tablets may impair fertility *[see Use in Specific Populations (8.3)]*.

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.apotex.com.

Rx only
APOTEX INC
AXITINIB TABLETS
1 mg and 5 mg

Manufactured By:	**Manufactured For:**
Apotex Inc.	Apotex Corp.
Toronto, Ontario	Weston, Florida
Canada M9L 1T9	33326

Rev. 3

PATIENT INFORMATION
Axitinib (ax i′ ti nib) **Tablets**

What are axitinib tablets?

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

- alone when 1 prior drug treatment regimen for your RCC has not worked.

It is not known if axitinib tablets are safe and effective in children.

Before taking axitinib tablets, 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 axitinib tablets for at least 2 days before planned surgery. See **"What are the possible side effects of axitinib tablets?"**

For females, tell your healthcare provider if you:

- are pregnant or plan to become pregnant. Taking axitinib tablets during pregnancy can harm your unborn baby. You should not become pregnant during treatment with axitinib tablets.
- are able to become pregnant. You should have a pregnancy test before you start treatment with axitinib tablets. Use effective birth control during treatment and for 1 week after your last dose of axitinib tablets. 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 axitinib passes into your breast milk. Do not breastfeed during treatment and for 2 weeks after your last dose of axitinib tablets.

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 axitinib tablets.
- If your female partner becomes pregnant during your treatment with axitinib tablets, 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. Axitinib tablets 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 axitinib tablets?

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

What should I avoid while taking axitinib tablets?

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

What are the possible side effects of axitinib tablets?

Axitinib tablets may cause serious side effects, including:

- **High blood pressure (hypertension). High blood pressure is common with axitinib tablets and may sometimes be severe.** Your healthcare provider should check your blood pressure regularly during treatment with axitinib tablets. 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 axitinib tablets.
- **Blood clots in your veins or arteries.** Axitinib tablets 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.** Axitinib tablets 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 axitinib tablets. 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 axitinib tablets:
  - 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 axitinib tablets. Tell your healthcare provider if you have any of the following symptoms during your treatment with axitinib tablets:
  - 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 axitinib tablets treatment. Tell your healthcare provider if you plan to have any surgery before starting or during treatment with axitinib tablets.
  - You should stop taking axitinib tablets at least 2 days before planned surgery.
  - Your healthcare provider should tell you when you may start taking axitinib tablets again after surgery.

- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** A condition called reversible posterior leukoencephalopathy syndrome (RPLS) can happen during treatment with axitinib tablets. 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 axitinib tablets. If you develop protein in your urine, your healthcare provider may decrease your dose of axitinib tablets or stop your treatment.
- **Liver problems.** Your healthcare provider will do blood tests before and during your treatment with axitinib tablets. Your healthcare provider may delay or stop your treatment with axitinib tablets if you develop severe liver problems. Tell your healthcare provider right way if you have any of the following symptoms:
  - yellowing of your skin or the whites of your eyes
  - severe nausea or vomiting
  - pain on the right side of your stomach area (abdomen)
  - dark urine (tea colored)
  - bleeding or bruising more easily than normal

The most common side effects of axitinib tablets when used alone include:

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

Axitinib tablets 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 axitinib tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store axitinib tablets?
Store axitinib tablets at room temperature between 68°F to 77°F (20°C to 25°C).
Keep axitinib tablets and all medicines out of the reach of children.

General information about the safe and effective use of axitinib tablets.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use axitinib tablets for a condition for which it was not prescribed. Do not give axitinib tablets 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 axitinib tablets that is written for health professionals.

What are the ingredients in axitinib tablets?
Active ingredient: axitinib
Inactive ingredients: croscarmellose sodium, ethylcellulose, magnesium stearate, and microcrystalline cellulose. The film coating contains hypromellose, iron oxide red, titanium dioxide, and triacetin.

For more information, go to www.apotex.com or call 1-800-706-5575

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

Rx only
AXITINIB TABLETS
1 mg and 5 mg

Manufactured By:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured For:
Apotex Corp.
Weston, Florida
33326

Rev. 3

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