Renaxen
Axitinib INN

Everest

COMPOSITION
RENAXEN 1 Tablet: Each film coated tablet contains Axitinib INN 1 mg.

RENAXEN 5 Tablet: Each film coated tablet contains Axitinib INN 5 mg.

PHARMACOLOGY
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.

Indication
Axitinib is a kinase inhibitor indicated:
• in combination with Avelumab, for the first-line treatment of patients with advanced Renal Cell Carcinoma (RCC).
• in combination with Pembrolizumab, for the first-line treatment of patients with advanced RCC.
• as a single agent, for the treatment of advanced Renal Cell Carcinoma (RCC) after failure of one prior systemic therapy.

Dosage and Administration
First-Line Advanced RCC
Axitinib in Combination with Avelumab
The recommended starting dosage of Axitinib is 5 mg orally taken twice daily (12 hours apart) with or without food in combination with Avelumab 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. When Axitinib is used in combination with Avelumab, dose escalation of Axitinib above the initial 5 mg dose may be considered at intervals of two weeks or longer.

Axitinib in Combination with Pembrolizumab
The recommended starting dosage of Axitinib is 5 mg orally twice daily (12 hours apart) with or without food in combination with Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity. When Axitinib is used in combination with Pembrolizumab, dose escalation of Axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer.

Second-Line Advanced RCC
As a single agent, the recommended starting oral dose is 5 mg twice daily. Administer Axitinib doses approximately 12 hours apart with or without food.

Important Administration Instructions
Advise patients to swallow Axitinib 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.

Dose Modification Guidelines
Dose increase or reduction is recommended based on individual safety and tolerability.
Recommended Axitinib dosage increases and reductions are provided in Table 1.
Over the course of treatment, patients who tolerate Axitinib for at least two consecutive weeks with no adverse reactions Grade >2 (according to the CTCAE), are normotensive, and are not receiving anti-hypertension medication, may have their dose increased.

Table 1: Recommended Dosage Increases and Reductions for Axitinib

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*	
First dose reduction**	3 mg twice daily
Second dose reduction	2 mg twice daily

* for management of adverse drug reactions
** from 5 mg twice daily

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

Table 2: Recommended Dosage Modification for Axitinib for Adverse Reactions

Adverse Reaction	Severity	Dosage Modifications for Axitinib
Hypertension	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	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	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	Any Grade	• The safety of resumption of Axitinib 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 Leukoence-phalopathy Syndrome	Any Grade	• Permanently discontinue
Proteinuria	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.

Table 3: Recommended Dosage Modification for Adverse Reactions for Axitinib in Combination with Avelumab or Pembrolizumab

Treatment	Adverse Reaction	Severity*	Dosage Modifications for Axitinib
Axitinib in combination with Avelumab OR Pembroli-zumab	Liver enzyme elevations**	ALT or AST at least 3 times ULN but less than 10 times ULN without concurrent total bilirubin at least 2 times ULN	Withhold both Axitinib and Avelumab or Pembrolizumab until resolution to Grades 0–1 Consider rechallenge with Axitinib and/or Avelumab or Pembrolizumab***
		ALT or AST increases to more than 3 times ULN with concurrent total bilirubin at least 2 times ULN or ALT or AST at least 10 times ULN	Permanently discontinue both Axitinib and Avelumab or Pembrolizumab
	Diarrhea	Grade 1–2	Initiate symptomatic medications.
		Grade 3	Interrupt Axitinib and initiate symptomatic medications. If diarrhea is controlled, Axitinib may be resumed at either the same dose or reduced by 1 dose level.
		Grade 4	Withhold Axitinib until resolution to Grade <2, then restart Axitinib dose reduced by 1 dose level
Axitinib in combination with avelumab	Major Adverse Cardio-vascular Events (MACE)	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal
*Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

**Consider corticosteroid therapy
***If rechallenging with Axitinib, consider dosage reduction per Table 1. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery.

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 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 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 dose should be returned (after 3 – 5 half-lives of the inhibitor) to that used prior to initiation of the strong CYP3A4/5 inhibitor.

Dosage Modification for Hepatic Impairment
No starting dose adjustment is required when administering Axitinib to patients with mild hepatic impairment (Child-Pugh class A). Based on the pharmacokinetic data, the Axitinib 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 has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hypertension
Common with Axitinib (40% incidence); manage with antihypertensive therapy. Monitor blood pressure before and during treatment. Discontinue or adjust dose for severe cases.
Arterial Thromboembolic Events
Rare but serious events (1% incidence); discontinue Axitinib if these occur.
Venous Thromboembolic Events: Higher incidence with Axitinib (3%); monitor for signs of VTE and PE. Withhold or discontinue based on severity.

Hemorrhage
Occurs in 16% of patients; withhold or discontinue for severe cases. Not recommended for patients with active brain metastases or gastrointestinal bleeding.

Cardiac Failure
Reported in 2% of patients; monitor for symptoms and adjust or discontinue treatment as needed.
Gastrointestinal Perforation/Fistula: Rare, but monitor for symptoms and manage appropriately.

Thyroid Dysfunction
Common (19% hypothyroidism); monitor thyroid function and manage accordingly.

Impaired Wound Healing
Withhold Axitinib before and after surgery. Discontinue if healing issues persist.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Rare (reported in <1% of patients). Discontinue permanently if RPLS develops.

Proteinuria
Occurs in 11% of patients; monitor protein levels and adjust dose for severe cases.

Hepatotoxicity
Monitor liver function. Higher risk when combined with Avelumab or Pembrolizumab; manage liver enzyme elevations and consider dose adjustments.
Cardiovascular Events: Increased risk with Axitinib + Avelumab combination (7% incidence). Monitor cardiovascular health and discontinue for severe events.

Embryo-Fetal Toxicity
Can cause fetal harm; advise women to avoid pregnancy and use contraception during and after treatment. Males should use contraception during and for 1 week after treatment.

ADVERSE REACTIONS
The most common adverse reactions were Hypertension, Arterial thromboembolic events, Venous thromboembolic events, Hemorrhage, Cardiac failure, Gastrointestinal perforation and fistula formation, Thyroid dysfunction, Reversible posterior leukoencephalopathy syndrome, Proteinuria, Hepatotoxicity, Hepatic impairment.

DRUG INTERACTIONS
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 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 dose should be reduced.

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 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 potentialis recommended. 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.

USE IN SPECIFIC POPULATIONS
Pregnancy
Axitinib can cause fetal harm based on animal studies. Advise females of reproductive potential to avoid pregnancy during treatment and use effective contraception. No human data available. Refer to Avelumab or Pembrolizumab prescribing information if used in combination

Lactation
Advise not to breastfeed during treatment and for 2 weeks after the last dose

Females and Males of Reproductive Potential
Axitinib can harm a fetus. Advise both males and females to use contraception during treatment and for 1 week after the last dose. It may impair fertility in both sexes

Pediatric Use
Safety and effectiveness in pediatric patients not established. Two small studies showed no new safety concerns, but exposure levels were lower than those in adults

Geriatric Use
No significant safety or efficacy differences were observed in patients ≥65 years old. No dosage adjustment needed for the elderly

Hepatic Impairment
For mild hepatic impairment (Child-Pugh class A), no dose adjustment needed. For moderate impairment (Child-Pugh class B), reduce starting dose. Not studied in severe hepatic impairment (Child-Pugh class C)

Overdosage
In clinical studies, high doses caused side effects like hypertension, seizures, and hemoptysis. If overdose occurs, withhold Axitinib and provide supportive care

PHARMACEUTICAL INFORMATION
Storage Condition
Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED
RENAXEN 1 Tablet: Each HDPE container contains 120 film coated tablets (each tablet contains Axitinib INN 1 mg) a silica gel desiccant and polyester coil with a child-resistant closure.

RENAXEN 5 Tablet: Each HDPE container contains 60 film coated tablets (each tablet contains Axitinib INN 5 mg) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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