DRUG NAME: Axitinib

SYNONYM(S):

COMMON TRADE NAME(S): INLYTA®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Axitinib is a second generation tyrosine kinase inhibitor.[1] It selectively inhibits vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3) thus blocking angiogenesis, tumour growth and metastases.[1,2] Axitinib has been reported to be 50-450 times more potent than first generation VEGFR inhibitors.[1]

PHARMACOKINETICS:

Oral Absorption	pH dependent solubility (reduced solubility with increase in pH); bioavailability: 58%; fat content in meals results in variable exposure	
Distribution	time to peak: 2.5-4 h; steady state within 2-3 days	
	cross blood brain barrier?	no information found
	volume of distribution	160 L
	plasma protein binding	>99%
Metabolism	primarily in the liver by CYP 3A4/5	
	active metabolite(s)	none specified
	inactive metabolite(s)	none specified
Excretion	urine	23%, as metabolites
	feces	41%, mainly unchanged
	terminal half life	2.5-6 h
	clearance	38 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Renal cell cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***Hypertension*** has been observed with axitinib; hypertension should be well controlled prior to starting treatment.[2]
- ***Arterial and venous thromboembolic events***, including transient ischemic attack, myocardial infarction, cerebrovascular accident and retinal artery occlusion, deep vein thrombosis and pulmonary embolus, have been reported with axitinib; use with caution in patients at risk for or who have a history of these events. ***Elevated hemoglobin*** may increase the risk of thromboembolic events.[2]

- ***Congestive heart failure*** has been observed with axitinib; use with caution in patients who are bradycardic or at risk for bradyarrhythmias or taking heart rate lowering drugs.[2]
- ***Hemorrhagic events*** have been reported with axitinib; axitinib is not recommended in patients with untreated brain metastasis, pulmonary embolus in the past 6 months, or active bleeding in the past 3 months.[2]
- ***Impaired wound healing*** has been associated with vascular endothelial growth factor (VEGF) inhibitors; hold axitinib 24 hours prior to surgery and re-initiate post-surgery based on clinical assessment of the wound site.[2]

Special populations: Axitinib is not recommended in ***patients under 18 years old***. Physeal dysplasia and odontopathies in growing incisors have been reported in animal studies.[2]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test or clastogenic in mammalian *in vitro* or *in vivo* chromosome tests. Axitinib is aneugenic in a mammalian *in vivo* chromosome test.[2]

Fertility: In mice, reduced fertility and embryonic viability were reported in females and reduced testicular weights, sperm density and count were observed in males.[2]

Pregnancy: FDA Pregnancy Category D.[1] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Animal studies have demonstrated an increased incidence of cleft palate and variations in skeletal ossification at sub-therapeutic levels.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[3]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (4-35%, severe <1%)[2,4]
	hemoglobin increase (10%)
	leukopenia (11%)[2,4]
	lymphopenia (33%, severe ≤3%)[2,4]
	neutropenia (6%)
	polycythemia (1%)
	thrombocytopenia (15%, severe <1%)[2,4]
cardiac	***congestive heart failure*** (<1%)
	myocardial infarction (<1%)
ear and labyrinth	tinnitus (3%)
endocrine	hypothyroidism (19%, severe <1%)
	hyperthyroidism (1%)
eye	***retinal vein/artery occlusion, thrombosis*** (≤1%)
gastrointestinal	*emetogenic potential: low*[5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	abdominal pain (8-14%, severe 1-2%)
	constipation (20%, severe ≤1%)
	diarrhea (55%, severe 1-10%)
	dyspepsia (10%)
	gastric hemorrhage (<1%); see paragraph following **Side Effects** table
	gastrointestinal perforation; fistula (<1%)
	glossodynia (3%)
	hemorrhoids (4%)
	nausea (32%, severe 1-2%)
	rectal hemorrhage (2%)
	stomatitis/mucosal inflammation (15%, severe ≤1%)
	vomiting (24%, severe 1-3%)
general disorders and administration site conditions	asthenia (21%, severe 1-5%)
	fatigue (39%, severe 1-11%)
investigations	AST/ALT increased (20-22%, severe <1%)
	alkaline phosphatase increase (30%, severe ≤1%)
	amylase increase (25%, severe ≤2%)
	creatinine increase (55%)
	hyperbilirubinemia (1%)
	lipase increase (3-27%, severe 1-4%)
	weight decrease (25%, severe ≤2%)
metabolism and nutrition	appetite decrease (34%, severe 1-5%)
	bicarbonate decrease (44%, severe <1%)
	dehydration (6%)
	hypercalcemia (3-6%)
	hyperglycemia (28%, severe ≤2%)
	hyperkalemia (15%, severe ≤3%)
	hypernatremia (17%, severe ≤1%)
	hypocalcemia (39%, severe 1%)
	hypoalbuminemia (15%, severe <1%)
	hypoglycemia (11%, severe <1%)
	hyponatremia (13%, severe 1-3%)
	hypophosphatemia (13%, severe ≤2%)
musculoskeletal and connective tissue	arthralgia (15%, severe 1%)
	myalgia (7%)
	pain in extremity (13%, severe <1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
nervous system	***cerebrovascular accident*** (<1%)
	dizziness (9%)
	dysgeusia (11%)
	headache (14%, severe ≤1%)
	reversible posterior leukoencephalopathy syndrome (<1%); see paragraph following **Side Effects** table
	transient ischemic attack (1%)
renal and urinary	***hematuria*** (3%); see paragraph following **Side Effects** table
	proteinuria (11%, severe ≤ 3%); may require dose reduction or temporary interruption of therapy
	renal failure (2%)
respiratory, thoracic and mediastinal	cough (15%, severe ≤1%)
	dysphonia (31%)
	dyspnea (15%, severe 1-2%)
	epistaxis (6%); see paragraph following **Side Effects** table
	hemoptysis (2%); see paragraph following **Side Effects** table
skin and subcutaneous tissue	alopecia (4%)
	dry skin (10%)
	erythema (2%)
	palmar-plantar erythrodysesthesia (27%, severe ≤5%)
	pruritus (7%)
	rash (13%, severe <1%)
vascular	***cerebral hemorrhage*** (<1%); see paragraph following **Side Effects** table
	hypertension (40%, severe 1-16%)[1,2]; see paragraph following **Side Effects** table
	hypertensive crisis (1%)
	deep vein thrombosis (1%)
	pulmonary embolism (2-3%, severe <1%)[1,2]

Adapted from standard reference[2] unless specified otherwise.

Hypertension is reported in 40% of patients on axitinib. Increased blood pressure has been reported as early as 4 days after starting axitinib, although median onset for hypertension is within the first month of treatment. Monitor for hypertension within one week of starting treatment and regularly thereafter. Hypertension may be treated with a combination of standard anti-hypertensive therapy and axitinib dose reduction or interruption. Patients on anti-hypertensive medications should be monitored for hypotension if axitinib is interrupted. Discontinue axitinib for hypertensive crisis or severe and persistent hypertension despite anti-hypertensive therapy.[2]

Reversible posterior leukoencephalopathy syndrome (RPLS), a rare neurologic disorder, has been reported with axitinib. Symptoms may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension, and may be difficult to differentiate from those of uncontrolled hypertension. Brain imaging is necessary to confirm diagnosis. Discontinue axitinib when signs/symptoms of RPLS are present. The safety of reinitiating treatment is not known.[2]

Hemorrhagic events, including cerebral hemorrhage, gastrointestinal hemorrhage, hematuria, hemoptysis, and epistaxis, have been associated with axitinib and are sometimes fatal. Any hemorrhage requiring medical intervention may require a temporary interruption of axitinib.[4]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
antacids[2]	may decrease plasma level of axitinib; may reduce pharmacological effect of axitinib	pH-dependent solubility (i.e., reduced axitinib solubility with increasing pH)	do not take antacids 2 hours before through 2 hours after axitinib.
bevacizumab[1]	no effect on axitinib or bevacizumab pharmacokinetics		
carboplatin[1]	no effect on axitinib or carboplatin pharmacokinetics		
cisplatin[1]	no effect on axitinib or cisplatin pharmacokinetics		
fluorouracil[1]	no effect on axitinib or fluorouracil pharmacokinetics		
gemcitabine[1]	no effect on axitinib or gemcitabine pharmacokinetics		
grapefruit and grapefruit juice[2]	may increase plasma level of axitinib	may inhibit CYP 3A4/5 metabolism of axitinib in the intestinal wall	avoid grapefruit and grapefruit juice
irinotecan[1]	no effect on axitinib or irinotecan pharmacokinetics		
ketoconazole[1,2]	axitinib AUC increased by 2-fold and C_{max} by 1.5-fold	inhibits CYP 3A4/5 metabolism of axitinib	avoid concurrent therapy if possible; otherwise consider a 50% dose reduction of axitinib
leucovorin[1]	no effect on axitinib or leucovorin pharmacokinetics		
oxaliplatin[1]	no effect on axitinib or oxaliplatin pharmacokinetics		
paclitaxel[1]	no effect on axitinib or paclitaxel pharmacokinetics		
phenytoin[1]	axitinib AUC and C_{max} reduced by approximately 10-fold	induces CYP 3A4/5 metabolism of axitinib	avoid concurrent therapy
rabeprazole[2]	axitinib AUC reduced by 15% and C_{max} by 42%	pH-dependent solubility (i.e., reduced axitinib solubility with increasing pH)	avoid concurrent use where possible; consider switch to antacids; **See** antacids interaction above

AGENT	EFFECT	MECHANISM	MANAGEMENT
rifampin[2]	axitinib AUC reduced by 79% and C_{max} by 71%	induces CYP 3A4/5 metabolism of axitinib	avoid concurrent therapy

Strong CYP 3A4/5 inhibitors may increase axitinib concentrations and drug toxicity. If concurrent therapy cannot be avoided, consider a 50% dose reduction for axitinib.[1] **Strong or moderate CYP 3A4/5 inducers** may reduce plasma concentration of axitinib, possibly resulting in its reduced effectiveness; avoid concurrent use if possible.[2]

In vitro studies have demonstrated that axitinib may inhibit **CYP 1A2,** resulting in increased plasma levels of CYP 1A2 substrates.[2]

Axitinib inhibits **P-glycoprotein** *in vitro*; however, this effect is not expected at therapeutic plasma concentrations.[2]

SUPPLY AND STORAGE:

Oral: Pfizer Products Inc. supplies axitinib as 1 mg and 5 mg tablets. Tablets contain lactose monohydrate. Store at room temperature.[2]

Additional information: For patients unable to swallow tablets, a solution may be given through a nasogastric tube. Dissolve whole tablets in 15 mL of USP-grade water in an amber-coloured syringe. Do not use tap or bottled water. Flush nasogastric tube with 15 mL USP-grade water before and after administration. Prepare dose just prior to administration. Do not expose to direct light.[1]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Oral:[2,6]
5 mg (range 2–10 mg) PO twice daily
Administer with food or on an empty stomach.

Concurrent radiation: no information found

Dosage in renal failure:[2] no dose adjustment is recommended for mild to severe renal impairment; no information found for end-stage renal disease

Dosage in hepatic failure:[2] modify according to protocol by which patient is being treated; if no guidelines available, the following has been suggested:

Degree of hepatic impairment	Dose
Mild (Child-Pugh class A)	no dose adjustment
Moderate (Child-Pugh class B)	consider a 50% dose reduction
Severe (Child-Pugh class C)	no information found

Dosage in dialysis: no information found

Children: no information found

REFERENCES:

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3. Christian Kollmannsberger MD. Personal communication. BC Cancer Agency Genitourinary Tumour Group; 10 January 2014.
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5. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
6. BC Cancer Agency. (UGUAXIT) BCCA Protocol Summary for Therapy for Metastatic Renal Cell Carcinoma of Using Axitinib. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2014.