**Drug Monograph**



## A - Drug Name

# aXitinib

**COMMON TRADE NAME(S):** Inlyta®

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## B - Mechanism of Action and Pharmacokinetics

Axitinib is an inhibitor of VEGF receptor tyrosine kinases 1, 2, and 3. These receptors are involved with pathologic angiogenesis, growth and metastases of cancer cells.

| | | |
|---|---|---|
| Absorption | Pharmacokinetics is dose proportional and linear. Daily dosing results in an approximately 1.4-fold accumulation compared with administration of a single dose. | |
| | Bioavailability | 58% |
| | Time to reach steady state | 2 to 3 days |
| Distribution | PPB | > 99%; mainly to albumin and moderate binding to alpha 1-acid glycoprotein |
| Metabolism | Metabolized mainly in the liver. Sulfoxide and N-glucuronide metabolites have been demonstrated to be ~ 400-fold and 8000-fold less potent *in vitro* respectively against VEGFR-2 compared with axitinib. | |
| Elimination | Urine | 23% (primarily carboxylic acid and sulfoxide metabolites) |
| | Feces | 41% (12% unchanged) |

| | |
|---|---|
| Half-life | 2.5 - 6.1 hours |

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## C - Indications and Status

**Health Canada Approvals:**

- Renal cell carcinoma

Refer to the product monograph for a full list and details of approved indications.

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## D - Adverse Effects

**Emetogenic Potential:** Minimal – No routine prophylaxis; PRN recommended

| ORGAN SITE | SIDE EFFECT* (%) | ONSET** |
|---|---|---|
| Auditory | Tinnitus (3%) | E |
| Cardiovascular | Arterial thromboembolism (1%) (including retinal) | E |
| | Artery aneurysm (rare) | E D L |
| | Artery dissection (rare) | E D L |
| | Bradycardia | E |
| | Cardiotoxicity (2%) (may be severe) | D |
| | Hypertension (40%) (1% grade 4) | E |
| | Venous thromboembolism (3%) | E |
| Dermatological | Alopecia (4%) | E |
| | Hand-foot syndrome (27%) (severe 5%) | E |
| | Rash (13%) | E |
| Gastrointestinal | Abdominal pain (14%) | E |
| | Anorexia, weight loss (34%) | E |
| | Constipation (20%) | E |

| | | |
|---|---|---|
| | Diarrhea (55%) | E |
| | Dyspepsia (10%) | E |
| | GI perforation (1%) (or fistula) | E |
| | Mucositis (15%) | E |
| | Nausea, vomiting (32%) | I |
| General | Fatigue (39%) | E |
| Hematological | Hemoglobin increased (10%) | E |
| | Hemorrhage (16%) (may be severe) | E |
| | Myelosuppression ± infection (15%) (may be severe) | E |
| Hepatobiliary | ↑ Amylase / lipase (27%) | E |
| | ↑ LFTs (22%) | E |
| Metabolic / Endocrine | Abnormal electrolyte(s) (17%) | E |
| | Hyperglycemia (28%) | E |
| | Hyperthyroidism (1%) | E D |
| | Hypoglycemia (11%) | E |
| | Hypothyroidism (19%) | E |
| Musculoskeletal | Musculoskeletal pain (15%) | E |
| Nervous System | Dizziness (9%) | E |
| | Dysgeusia (11%) | E |
| | Headache (14%) | E |
| | Posterior reversible encephalopathy syndrome (PRES) (<1%) | E |
| Renal | Creatinine increased (55%) (2% severe) | E |
| | Proteinuria (11%) | E |
| Respiratory | Cough, dyspnea (15%) | E |
| | Hoarseness (31%) | E |

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for axitinib include diarrhea, hypertension, fatigue, anorexia, weight loss, lymphopenia, nausea and vomiting.

**Hypertension** is common and may be severe. It must be controlled prior to starting treatment and monitored carefully with axitinib dose modifications. (Refer to Management of Angiogenesis Inhibitor (AI)-Induced Hypertension.) Cardiac effects are more common than with sunitinib and may be fatal.

**Reversible Posterior Leukoencephalopathy Syndrome** may present with headache, seizure, lethargy, confusion, blindness and potentially other visual and neurologic disturbances. It may also be associated with mild to severe hypertension.

Severe cases of **artery dissection** (with or without hypertension) and **artery aneurysm** (including rupture) have been reported in patients using VEGFR TKIs.

**Hemorrhages** occurred during the pivotal trial. These hemorrhagic events included cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal hemorrhage and melena. Axitinib should be used with caution in patients with significant risk for bleeding events. For patients with untreated brain metastases, history of pulmonary embolism in previous 6 months, or with a history of active bleeding in the previous 3 months, it is not recommended to administer axitinib.

**Gastrointestinal perforation, including death and gastrointestinal fistulas** have been reported.

**Arterial and venous thromboembolisms** have been reported. Clinical trials excluded patients who had recent arterial (within 1 year) and venous (within 6 months) thromboses.

**Thyroid dysfunction** has been reported in the pivotal trial. Events involving both hypothyroidism and hyperthyroidism have occurred.

**Hand-foot syndrome** may be severe and present with redness and pain on the palms of the hands and soles of the feet. It may occur on other areas of the body surface. Prevention of hand-foot syndrome includes control of calluses and minimizing pressure stress to soles and palms. Consider initiating treatment with topical therapies as soon as symptoms occur. Management may include the use of keratolytic creams (e.g. urea, salicylic acid, or alpha hydroxyl acid-based creams applied sparingly only on hyperkeratotic areas) and moisturizing creams (applied liberally) for symptomatic relief.

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## E - Dosing

Refer to protocol by which patient is being treated.

**Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the hepatitis B virus screening and management guideline.

Do not start treatment until any hypertension is controlled and platelets are ≥ 100 x $10^9$/L and ANC ≥ 1.5 x $10^9$/L.

Correct electrolyte abnormalities prior to treatment, especially potassium, calcium and magnesium.

Hold axitinib for at least 24 hours prior to planned surgery. Re-start post-surgery based on clinical assessment of wound healing.

***Adults:***

**Oral:** 5 mg twice daily; may be titrated up to a maximum of 10 mg twice daily according to tolerance

***Dosage with Toxicity:***

| Dose Level | Dose |
|---|---|
| +2 | 10 mg BID |
| +1 | 7 mg BID* |
| **0 (starting dose)** | **5 mg BID*** |
| -1 | 3 mg BID |
| -2 | 2 mg BID |

*May ↑ 1 dose level in patients who tolerate (≤ grade 2 toxicity) the current dose for 2 consecutive weeks, with no prior dose modification, normotensive and do not require antihypertensive medications

Do not re-escalate a dose reduced for toxicity.

| Toxicity | Action |
|---|---|
| Grade 3 related organ / non-hematologic | Hold*; ↓ 1 dose level |
| Moderate or severe proteinuria | ↓ 1 dose level<br><br>Consider temporary discontinuation of therapy in severe proteinuria* |
| Hypertension | Treat appropriately (refer to Management of Angiogenesis Inhibitor (AI)-Induced Hypertension). Reduce dose or hold as appropriate. |
| Grade 4 related organ/ non-hematologic; uncontrolled hypertension/crisis; RPLS; heart failure; wound dehiscence | Discontinue |

*Do not start new cycle until toxicities have recovered to ≤ grade 2, platelets ≥ 100 x $10^9$/L, and ANC ≥ 1.5 x $10^9$/L.

### Dose Modification for Hepatotoxicity in Combination with Pembrolizumab

| ALT or AST | | Bilirubin | Action |
|---|---|---|---|
| ≥ 3 to < 10 x ULN | And | < 2 X ULN | Hold pembrolizumab and axitinib until ≤ grade 1.<br><br>Consider corticosteroids.<br><br>After recovery, consider re-challenge with a single drug or sequentially with both drugs. Consider dose reduction if rechallenging with axitinib. |
| > 3 x ULN | And | ≥ 2 x ULN | Discontinue both drugs. |
| ≥ 10 x ULN | And | Any | Consider corticosteroids. |

***Dosage with Hepatic Impairment:***

Axitinib exposure is increased in moderate hepatic impairment, but has not been studied in patients with severe impairment.

| **Hepatic impairment** | **Starting dose** |
|---|---|
| Mild hepatic impairment (Child-Pugh class A) | No dose adjustment required |
| Moderate hepatic impairment (Child-Pugh class B) | ↓ dose by approximately 50% |
| Severe hepatic impairment (Child-Pugh class C) | Do not use (no data) |

Higher than expected incidences of severe LFT elevations have been reported in axitinib in combination with pembrolizumab.

***Dosage with Renal Impairment:***

| **Creatinine Clearance (mL/min)** | **Dose** |
|---|---|
| 15 - 89 | No dosage adjustments required. |
| < 15 | Use with caution. |

***Dosage in the elderly:***

No dosage adjustments required.

***Children:***

Axitinib should not be administered to children under 18 years of age. Safety and effectiveness in pediatric patients have not been established. Angiogenesis inhibitors are expected to result in a number of issues in pediatric patients including physeal dysplasia.

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## F - Administration Guidelines

- Tablets should be swallowed whole with a glass of water, with or without food.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during treatment.
- If a dose is missed, patient should skip the missed dose and take the next dose at the next scheduled time.
- Store at room temperature (25°C). Excursions permitted to 15-30°C.

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## G - Special Precautions

### Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

### Other Warnings/Precautions:

- Use with caution in patients at risk of or who have a history of arterial or venous thromboembolism.
- Use with caution in patients at risk of bleeding. Axitinib is not recommended for use in patients with untreated brain metastases, a history of pulmonary embolism in the past 6 months, or active bleeding in the past 3 months.
- Use axitinib with caution in bradycardic patients or patients at risk of bradyarrhythmia.
- Clinical trials excluded patients with uncontrolled hypertension at baseline or a recent history of MI, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident, TIA, deep vein thrombosis or pulmonary embolism.
- Tablets contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

### Other Drug Properties:

- Carcinogenicity: Unknown

**Pregnancy and Lactation:**

- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
- Mutagenicity: No
- Genotoxicity: Yes
- Clastogenicity: No
  Axitinib should not be used in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 week** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for at least **2 weeks** after the last dose.
- Fertility effects: Probable

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## H - Interactions

Axitinib is metabolized primarily by CYP3A4/5. It is metabolized to a lesser extent by CYP 1A2, CYP2C19 and UGT1A1.

Axitinib is not expected to inhibit the metabolism drugs that are substrates of CYP2A6, 2C9, 2C19, 2D6, 2E1, 3A4/5, UGT1A1 or P-glycoprotein, nor induce CYP1A1, 1A2 or CYP3A4/5.

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| CYP3A4/5 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges, starfruit, etc.) | ↑ axitinib exposure and/or toxicity | ↓ metabolism of axitinib | Avoid strong inhibitors if possible; axitinib dose reduction recommended if co-administration with potent inhibitors is necessary |
| CYP3A4/5 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc) | ↓ axitinib concentration and/or efficacy | ↑ metabolism of axitinib | Avoid strong inducers and, if possible, moderate inducers |
| Drugs that increase gastric pH (e.g. antacids, PPI, H2 antagonists) | ↓ axitinib exposure | ↓ exposure with increased pH | Caution; avoid these agents 2 hours before to 2 hours after axitinib is administered |
| CYP1A2 substrates (e.g. theophylline) and CYP2C8 substrates (e.g. paclitaxel, sorafenib) | Potentially ↑ substrate exposure | Axitinib has potential to inhibit CYP1A2 and CYP2C8 | Caution; monitor for drugs with narrow therapeutic range |

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## I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

### Recommended Clinical Monitoring

| Monitor Type | Monitor Frequency |
|---|---|
| CBC | Baseline and at each visit |
| Blood pressure | Baseline and at each visit; start within a week after beginning treatment, more frequent after dose changes or interruptions |
| Liver function tests (ALT, AST and bilirubin) | Baseline and at each visit (consider more frequent monitoring when used in combination with pembrolizumab) |
| Renal function tests | Baseline and at each visit |
| Thyroid function tests | Baseline and as clinically indicated |
| Proteinuria | Baseline and as clinically indicated |
| Signs and symptoms of cardiotoxicity | Baseline and periodically during treatment |
| Clinical toxicity assessment for bleeding, thromboembolism, neurological and GI effects | At each visit |

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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## J - Supplementary Public Funding

**Exceptional Access Program (EAP Website)**

- aXitinib - For second or third line treatment of advanced renal cell carcinoma, according to clinical criteria
- aXitinib - In combination with pembrolizumab for first-line advanced or metastatic renal cell carcinoma

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## K - References

Fischer A, Wu SH, Ho AL, et al. The risk of hand-foot skin reaction to axitinib, a novel VEGF inhibitor: a systematic review of literature and meta-analysis. Invest New Drugs 2013;31:787-97.

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Rini BI, Plimack ER, Stus V, et al. KEYNOTE-426 Investigators. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380(12):1116-27.

Rini BI et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011;378:1931-9.

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van Leeuwen RW, van Gelder T, Mathijssen RH, et al. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. Lancet Oncol. 2014;15(8):e315-e326.

**April 2024** Updated Pregnancy and Lactation section

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## L - Disclaimer

*Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.*

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