Drug Monograph

A - Drug Name

vanDETanib

COMMON TRADE NAME(S): Caprelsa®

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B - Mechanism of Action and Pharmacokinetics

Vandetanib is an inhibitor of multiple tyrosine kinase families, including VEGFR-2 (vascular endothelial growth factor receptor-2), EGFR (epidermal growth factor receptor), and the RET (rearranged during transfection) proto-oncogene, which affects angiogenesis and cell survival. Approval in unresectable thyroid cancer is based on a significant improvement in progression-free survival at 2 years versus placebo. No significant difference in overall survival has been observed. Vandetanib is only available through a restricted distribution program.

Absorption	Peak plasma concentrations reached at 6 hours after dosing. Accumulation is seen on multiple dosing with steady state achieved from approximately 2-3 months. Pharmacokinetics are linear within the usual dosing range. Vandetanib exposure is not affected by a meal. Limited data suggested that Chinese and Japanese patients had higher average drug exposure than Caucasian patients.	
Distribution	PPB	94%
Metabolism	Metabolized by CYP3A4 to N-desmethyl vandetanib and by monooxygenase enzymes FMO1 and FMO3 to vandetanib-N-oxide. Glucuronide conjugate is a minor metabolite.	
	Active metabolites	N-desmethyl vandetanib
	Inactive metabolites	vandetanib-N-oxide and others
Elimination	Within 21 days, about 69% of a dose is recovered in feces (44%) and in urine	

	(25%). Due to the long half-life of the drug, elimination may continue beyond 21 days. Vandetanib may inhibit its renal excretion via hOCT2. No clear difference in clearance with respect to age and gender.
	Half-life 19 days

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C - Indications and Status

Health Canada Approvals:

- Thyroid cancer

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

Vandetanib can only be prescribed and dispensed by physicians and pharmacies under certification by the Caprelsa® restricted distribution program.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (1%)	E
	Artery aneurysm (rare)	E D L
	Artery dissection (rare)	E D L
	Cardiotoxicity (heart failure < 1%)	D
	Hypertension (32%) (2% severe)	E
	QT interval prolonged (14%) (± arrhythmia)	E
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (<10%)	E
	Nail disorder (<10%)	E

	Photosensitivity (13%)	E
	Rash (45%) (may be severe - SJS, TEN)	E
Gastrointestinal	Abdominal pain (14%)	E
	Anorexia, weight loss (21%)	E
	Diarrhea (56%) (11% severe)	E
	Dyspepsia (11%)	E
	GI perforation (rare)	E
	Mucositis (<1%)	E
	Nausea, vomiting (33%)	I
General	Delayed wound healing	E
	Fatigue (24%)	E
Hematological	Hemorrhage (<1%)	E
	Myelosuppression ± infection, bleeding (10%)	E
Hepatobiliary	↑ LFTs (51%)	E
	Pancreatitis (rare)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (57%) (↑/↓ Ca, ↓K, ↓Na, Mg)	E
	Hypothyroidism (49%)	E
Nervous System	Depression (1%)	E
	Headache (26%)	E
	Insomnia (13%)	E
	Posterior reversible leukoencephalopathy syndrome (PRES) (<1%)	E
	Tremor (<10%)	E
Ophthalmic	Other - corneal opacity (5%)	E
Renal	Nephrotoxicity (17%) (may be severe)	E
Respiratory	Cough (11%)	E
	Pneumonitis (<1%)	D

* "*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 vandetanib include abnormal electrolyte(s), diarrhea, ↑ LFTs, abdominal pain, rash, nausea/vomiting, hypertension, headache and fatigue.

QT prolongation appears to be dose-dependent. The average change from baseline was 35ms and 7% of patients had QTcF > 500 ms. Due to the 19 day half-life, QT prolongation may not resolve quickly. Serum potassium should be maintained at 4 mEq/L or higher; magnesium and calcium levels should be kept within normal range. Hypertensive crisis has been observed. Cardiotoxicity has been reported and may not be reversible after vandetanib discontinuation.

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

LFTs usually resolve while continuing treatment with vandetanib, while others usually recover after withholding treatment for 1-2 weeks.

Vandetanib slows but does not prevent **wound healing**. The appropriate time period between discontinuing vandetanib and subsequent surgery is not known.

Patients taking vandetanib have a potential for **photosensitivity** upon sun exposure. Patients should wear protective clothing and/or sunblock during vandetanib treatment and for 4 months after the last dose.

Fatal cases of **hemorrhage, hepatic failure, skin reactions** or **ILD** have been reported.

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E - Dosing

Refer to protocol by which patient is being treated. Potassium, calcium and magnesium levels should be corrected before starting treatment.

Patients should be provided with loperamide and instructions on how to manage diarrhea.

Hold vandetanib for at least 1 month before elective surgery. Do not administer vandetanib for at least 2 weeks after major surgery and until adequate wound healing.

Adults:

Oral: 300 mg Daily

Dosage with Toxicity:

Dose levels: 300 mg daily; 200 mg daily; 100 mg daily

Toxicity	Action for Vandetanib
Grade 1 or 2 skin reactions	Treat symptomatically or by ↓ dose
Grade 3 or 4 skin toxicity	Treat symptomatically and hold until ≤ grade 1, then ↓ 1 dose level or Discontinue if Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis or grade 4
Grade 3 or 4 hypertension	Hold; control blood pressure medically. Consider ↓ dose
Grade 1 or 2 diarrhea	Treat symptomatically with loperamide and hydration.
Grade 3 or 4 diarrhea	Hold until grade 1, then ↓ 1 dose level.
Hemoptysis (≥ 2.5mL)	Hold until resolved. Consider discontinuing
QTcF ≥ 500 ms	Hold until QTcF <450 ms then ↓ 1 dose level; consider cardiology consult
Radiological changes suggestive of pneumonitis	Investigate. If mild may continue treatment ± corticosteroids / antibiotics during investigation; otherwise hold. If pneumonitis confirmed, discontinue.
Signs of symptoms of hypothyroidism	Adjust thyroid replacement therapy. Monitor TSH.
Grade 3 or 4 LFTs	Hold until grade 1. Consider ↓ dose.
• Severe arterial thromboembolism • Severe heart failure • RPLS • Severe bleeding	Discontinue
Other grade 3 or 4 related organ toxicity	Hold until grade 1, then ↓ 1 dose level.

Dosage with Hepatic Impairment:

Not recommended for use in patients with moderate and severe hepatic impairment (Child Pugh B and C). Limited data exist in patients with bilirubin >1.5 x ULN.

Dosage with Renal Impairment:

Vandetanib is not recommended for use in patients with severe renal impairment (clearance below 30 mL/min).

Exposure is increased in patients with renal impairment. The patient and QTcF must be closely monitored.

Creatinine Clearance (mL/min)	Starting Daily Dose
≥ 50	300 mg
30-49	200 mg
<30	Not recommended for use

Dosage in the elderly:

No adjustment in starting dose is required. Limited data in patients over 75 years of age.

Children:

No pediatric indications. Safety and efficacy have not been established.

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F - Administration Guidelines

- Vandetanib may be taken with or without meals
- Avoid products and juices containing grapefruit, star fruit, pomegranate, Seville oranges or other similar fruits that can inhibit CYP3A4.
- Take the dose at about the same time each day. Swallow whole; do not crush or chew.
- If the patient has difficulty swallowing the tablet(s), may mix it with water as follows:
  - a) Put the whole tablet into half a glass (50mL) of non-carbonated water. Do not use other liquids.
  - b) Stir the water until the tablet disintegrates. This may take about 10 minutes.
  - c) Drink the mixture immediately.
  - d) Rinse the empty glass well with another half a glass of water and drink it.
  - e) (This liquid mixture can also be given through nasogastric or gastrostomy tubes.)
- If a dose is missed, give it if it is within 12 hours from the missed dose, otherwise skip and give the next dose as scheduled.
- Store vandetanib at room temperature.

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G - Special Precautions

Contraindications:

- Congenital long QT syndrome or with a persistent QTcF of ≥500ms.
- Uncorrected hypokalemia, hypomagnesemia or hypocalcemia
- Uncontrolled hypertension or heart failure
- Patients with a recent history of hemoptysis of ≥ half teaspoon of red blood, or patients with moderate or severe hepatic impairment
- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Do not give vandetanib to patients with a history of Torsade de Pointes (unless all risk factors have been corrected), bradyarrhythmias or uncompensated heart failure.
- Patients must avoid sun exposure for 4 months after the last dose of vandetanib
- Vandetanib can only be prescribed or dispensed by physicians and pharmacies who have been certified under the Caprelsa® restricted distribution program. Patients must enrol and comply with the requirements of this program before receiving vandetanib.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Fetotoxicity: Documented in animals

- Embryotoxicity: Documented in animals
- Teratogenicity: Documented in animals
- Fertility effects: Probable
  Vandetanib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 3 months (for women) and 2 months (for men) after the last vandetanib dose.
- Mutagenicity: No
- Clastogenicity: No
- Genotoxicity: No
- Excretion into breast milk: Yes
  Breastfeeding is not recommended.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs that may prolong QT (i.e. Amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT prolongation	Additive	Avoid; if no alternative treatment exists, close QT monitoring should be performed
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ vandetanib concentration and exposure	↑ metabolism of vandetanib	Avoid; consider alternative drugs
CYP3A4 inhibitors (i.e. ketoconazole,	↑ vandetanib exposure and ↓ clearance (theoretical)	↓ metabolism of vandetanib	Avoid; consider alternative drugs

voriconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges, starfruit or pomegranate)			
Cisplatin	↑ cisplatin exposure	Possible accumulation of total platinum	Caution
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	Potential to ↑ exposure of Pgp substrates (up to 23% for digoxin)	Vandetanib inhibits Pgp	Caution; monitor closely; substrate dose adjustment may be required
OCT2 substrates (e.g. metformin)	Potential to ↓ elimination or ↑ exposure (up to 74%) of drugs excreted by OCT2	Vandetanib inhibits OCT2	Caution; monitor closely; substrate dose adjustment may be required

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
QTcF and blood pressure	at baseline, 2-4 weeks and 8-12 weeks during treatment, and q3 months thereafter, also after dose adjustments
Electrolytes (including calcium, potassium, magnesium) and TSH	at baseline, 2-4 weeks and 8-12 weeks during treatment, then q3 months thereafter, also after dose adjustments
Liver function tests	Baseline and regular
Clinical toxicity assessment for rash, hypertension, wound healing, diarrhea, arterial/venous thromboembolism, bleeding, neurologic, cardiovascular, ophthalmic and respiratory side effects	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Renal function tests	Baseline and regular

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- vanDETanib - Monotherapy for symptomatic and/or progressive medullary thyroid cancer (MTC), with specific criteria

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K - References

Product Monograph: Caprelsa® (vandetanib). AstraZeneca Canada, December 2016 and April 2022.

Product Monograph: Caprelsa® (vandetanib). AstraZeneca US, June 2011.

Product Monograph Update: Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs). Health Canada InfoWatch, June 2020.

Commander H, Whiteside G, Perry C. Vandetanib: first global approval. Drugs 2011;71(10):1355-68.

Martin P, Oliver S, Robertson J, et al. Pharmacokinetic drug interactions with vandetanib during coadministration with rifampicin or itraconazole. Drugs R D 2011;11(1):37-51.

July 2022 Modified Dose modifications and Dosage in renal impairment sections

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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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