DRUG NAME: Vandetanib

SYNONYM(S): ZD6474[1]

COMMON TRADE NAME(S): CAPRELSA®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Vandetanib is a potent, oral, selective inhibitor of multiple tyrosine kinases, including vascular endothelial growth factor receptor-2 (VEGFR-2), epidermal growth factor receptor (EGFR), and rearranged during transfection (RET) receptor tyrosine kinases. *In vivo*, vandetanib reduces tumour cell-induced angiogenesis, tumour vessel permeability, and inhibits tumour growth and metastases.[2,3]

PHARMACOKINETICS:

Oral Absorption	slow oral absorption, unaffected by food; time to peak = 4-10 h[1,2]	
Distribution	binds to human serum albumin and α1-acid-glycoprotein	
	cross blood brain barrier?	yes; penetration restricted by both BCRP1 and P-gp mediated active efflux[4]
	volume of distribution	7450 L
	plasma protein binding	90%
Metabolism	hepatic metabolism by CYP 3A4 and flavin-containing monooxygenase enzymes (FMO1, FMO3)[1]	
	active metabolite(s)	N-desmethyl-vandetanib, vandetanib N-oxide[1]
	inactive metabolite(s)	glucuronide conjugate
Excretion	slow excretion (69% of dose recovered after 21 days)	
	urine	25%
	feces	44%
	terminal half life	19 days
	clearance	13.2 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Thyroid cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- congenital long QT syndrome[2,3] or persistent QTc interval ≥ 500 milliseconds[2]

Caution:

- vandetanib can cause ***QTc prolongation***; correct preexisting electrolyte abnormalities and avoid concomitant drugs known to prolong the QT interval[2]

- severe ***hypertension*** and hypertensive crisis are reported; control preexisting hypertension prior to treatment[2]
- risk of ***hemorrhage*** is increased; hold vandetanib for recent hemoptysis[2]

Carcinogenicity: no information found

Mutagenicity: not mutagenic in Ames test. Vandetanib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: In animal studies, estrus cycle irregularity plus reduced pregnancy incidence, increased post-implantation loss, and reduced corpora lutea were reported. There were no reported effects on male fertility in animals; however, untreated female subjects mated with males receiving vandetanib had slightly increased pre-implantation losses and a reduced number of live embryos.[2]

Pregnancy: In animal studies, vandetanib was embryotoxic, fetotoxic, and teratogenic at doses equal to or lower than the recommended human dose. Increased embryo-fetal loss, decreased fetal birth weight, heart vessel malformations, and skeletal variations were observed. Female patients should use contraception during treatment and for three months after completing therapy. Male patients should use contraception during treatment and for two months after completing therapy.[2,3]

Breastfeeding: Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, vandetanib is distributed into milk and detected in infant plasma.[2]

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.[5,6] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.[7]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	neutropenia (10%, severe <1%)
	thrombocytopenia (9%)
cardiac	heart failure (<1%); may not be reversible upon discontinuation
endocrine	hypothyroidism (6%)
eye	blurred vision (9%)
	corneal abnormalities, including opacity (5-13%)[2,3]
gastrointestinal	*emetogenic potential:* low[8]
	abdominal pain (21%, severe 3%)
	diarrhea/colitis (57%, severe 11%); see paragraph following **Side Effects** table
	dry mouth (9%)
	dyspepsia (11%)
	intestinal perforation (<1%)
	nausea (33%, severe 1%)
	pancreatitis (<1%)
	vomiting (15%, severe 1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
general disorders	fatigue (24%, severe 6%)
hepatobiliary	hepatic failure (<1%)[2]; reported in patients with pre-existing hepatic disease
infections and infestations	upper respiratory tract infections (23%)
investigations	ALT increase (51%, severe 2%); usually resolves with continued treatment or brief (1-2 week) treatment interruption
	AST increase (30%)[2]
	creatinine increase (16%)
	QTc interval prolongation (14%, severe 8%); see paragraph following **Side Effects** table
metabolism and nutrition	appetite decrease (21%, severe 4%)
	hypocalcemia (57%, severe 6%)
	hypoglycemia (24%)
	hypomagnesemia (7%, severe <1%)
musculoskeletal and connective tissue	muscle spasms (6%)
nervous system	cerebrovascular ischemia (1%)[2]
	dysgeusia (8%)
	headache (26%, severe 1%)
	posterior reversible encephalopathy syndrome (<1%)[2]
psychiatric	depression (10%, severe 2%)
renal and urinary	proteinuria (10%)
respiratory, thoracic and mediastinal	interstitial lung disease (<1%)[2]
	pneumonitis (<1%)[2]
skin and subcutaneous tissue (see paragraph following **Side Effects** table)	alopecia (8%)
	dermatitis acneiform/acne (35%, severe 1%)
	dry skin (15%)
	nail abnormalities (9%)
	palmar-plantar erythrodysesthesia syndrome (1-10%)[2,9,10]
	photosensitivity reaction (13%, severe 2%)
	pruritis (11%, severe 1%)
	rash (53%, severe 5%); including Stevens-Johnson Syndrome and toxic epidermal necrolysis
vascular	hemorrhage (<1%)[2]; may be fatal
	hypertension (33%, severe 9%); including accelerated hypertension and hypertensive crisis

Adapted from standard reference[3] unless specified otherwise.

Dermatologic toxicity is commonly reported, ranging from mild to moderate toxicities such as rash, dermatitis acneiform, dry skin, pruritus, and palmar plantar erythrodysesthesia syndrome to more serious/fatal toxicities such

as Stevens Johnson syndrome and toxic epidermal necrolysis. Treat mild to moderate skin toxicity with symptomatic management such as topical corticosteroids, topical antibiotics, and oral antihistamines or consider vandetanib dose reduction. Treatment options for severe reactions include interruption or discontinuation of vandetanib treatment and/or systemic antibiotics plus topical and systemic corticosteroids. Vandetanib may cause ***photosensitivity***; therefore, effective sunblock and protective clothing is recommended during treatment and for four months after stopping therapy.[2,11]

Diarrhea commonly occurs and can be managed with routine anti-diarrheal medications. For severe diarrhea, interrupt vandetanib treatment and monitor serum electrolytes and ECG to enable early detection of QT prolongation which may occur secondary to dehydration. When diarrhea symptoms improve, vandetanib may be resumed at a reduced dose.[2,11]

QT interval prolongation, torsades de pointes, and sudden death are associated with vandetanib. QT prolongation appears to be dose-dependent and may persist for the duration of therapy. The reported mean increase in QTc interval from baseline is 35 milliseconds; however, increases greater than 60 milliseconds from baseline as well as QTc intervals of greater than 500 milliseconds have also been reported. To reduce the risk of QT prolongation, monitor ECG, electrolytes, and thyroid function, especially following dose adjustments. Correct electrolyte abnormalities and maintain serum potassium in high normal range and avoid concurrent therapy with other QT prolonging drugs. Due to the long half-life of vandetanib, a prolonged QTc interval may not resolve quickly. In the event of a QTc interval of 500 milliseconds or greater, interrupt vandetanib treatment and consider resuming at a reduced dose once the QTc is less than 450 milliseconds.[2]

Impaired ***wound healing*** has been associated with vascular endothelial growth factor (VEGF) inhibitors; however, this effect was not reported in patients who underwent surgery while on vandetanib. There is some evidence to suggest that vandetanib may delay, but not prevent wound healing. The appropriate time interval lapse required between discontinuing vandetanib and subsequent surgery is not known. Patients should be evaluated for wound healing before restarting vandetanib.[2,6]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
digoxin[2]	increased digoxin AUC by 23% and C_{max} by 29%	inhibition of P-glycoprotein (P-gp) by vandetanib	monitor for digoxin toxicity; adjust digoxin dose as indicated
grapefruit juice[2]	may increase plasma level of vandetanib	may inhibit CYP 3A4 metabolism of vandetanib in the intestinal wall	avoid grapefruit juice while on vandetanib
itraconazole[2,3,11]	increased vandetanib AUC by 9% and decreased clearance by 12%	strong inhibition of CYP 3A4 by itraconazole	avoid concurrent use if possible; monitor for increased vandetanib toxicity
metformin[2]	increased metformin AUC by 74% and C_{max} by 50%; decreased metformin clearance by 52%	inhibition of organic cation transporter 2 (OCT2) by vandetanib	monitor blood sugars and adjust metformin dose as indicated; effects may be delayed
omeprazole[2]	decreased vandetanib C_{max} by 15%; no effect on AUC	pH dependent solubility	no dose adjustment necessary
rifampin[2]	decreased vandetanib AUC by 40%; 2-fold increase in systemic clearance	strong induction of CYP 3A4 by rifampin	avoid concurrent use

Concurrent therapy with drugs that prolong QT/QTc interval or disrupt electrolyte levels should be avoided if possible; periodic monitoring of ECG and electrolytes is suggested.[12]

SUPPLY AND STORAGE:

Oral: Sanofi Genzyme supplies vandetanib as 100 mg and 300 mg tablets. Store at room temperature.[2]

Additional information:
- Vandetanib is available through the CAPRELSA® Restricted Distribution Program.[2]
- For patients who have difficulty swallowing, tablets may be dispersed in 50 mL of non-carbonated water only. Other liquids should not be used. Stir the tablet and water for approximately 10 minutes to disperse; tablets will not completely dissolve. The resulting dispersed preparation should be consumed immediately. Following consumption of the dose, the cup should be rinsed with water and the rinse contents also consumed to ensure administration of the full dose. The dispersion may be administered through nasogastric or gastrostomy tubes.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral[2,13]: ***300 mg*** (range 100-300 mg) ***PO once daily***

Administer with food or on an empty stomach.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated

Dosage in renal failure[2,11]: modify according to protocol by which patient is being treated; if no guidelines are available, the following dose adjustment may be used:

Creatinine clearance (mL/min)	Dose
≥50	300 mg daily
<50	200 mg daily[†]

[†]monitor QTc interval closely

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* for males N=1.23; for females N=1.04

Dosage in hepatic failure[2]*:* mild impairment: no adjustment required[2]
moderate/severe impairment (Child Pugh B or C): no information found; however, vandetanib use is not recommended in this group due to observed increases in Vd and prolonged T½

Dosage in dialysis: no information found

Children: safety and effectiveness not established in children

REFERENCES:

1. Cooper MR, Yi SY, Alghamdi W, et al. Vandetanib for the treatment of medullary thyroid carcinoma. Ann Pharmacother 2014;48(3):387-394.
2. Sanofi Genzyme. CAPRELSA® product monograph. Mississauga, Ontario; 8 December 2016.
3. AstraZeneca. CAPRELSA® full prescribing information. Wilmington, DE, USA; July 2016.
4. Minocha M, Khurana V, Qin B, et al. Co-administration strategy to enhance brain accumulation of vandetanib by modulating P-glycoprotein (P-gp/Abcb1) and breast cancer resistance protein (Bcrp1/Abcg2) mediated efflux with m-TOR inhibitors. Int.J.Pharm. 2012;434(1–2):306-314.
5. Karen Mason BSc(Pharm). Personal communication. BC Cancer Agency Head & Neck Tumour Group; 5 June 2017.
6. Cheryl Ho MD. Personal communication. BC Cancer Agency Head and Neck Tumour Group; 11 September 2017.
7. Wells SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30(2):134-141.
8. 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.
9. Harter P, Sehouli J, Kimmig R, et al. Addition of vandetanib to pegylated liposomal doxorubicin (PLD) in patients with recurrent ovarian cancer. A randomized phase I/II study of the AGO Study Group (AGO-OVAR 2.13). Invest New Drugs 2013;31:1499-1504.
10. Hsu C, Yang T, Huo T, et al. Vandetanib in patients with inoperable hepatocellular carcinoma: A phase II, randomized, double-blind, placebo-controlled study. J.Hepatol. 2012;56(5):1097-1103.
11. Lexicomp Online®: (database on the Internet). Vandetanib. Lexi-Comp Inc., 1 April 2017. Available at: http://online.lexi.com. Accessed 3 April 2017.
12. Pfizer Canada Inc. BOSULIF® product monograph. Kirkland, Quebec; 29 July 2015.
13. BC Cancer Head and Neck Tumour Group. (UHNOTVAN) BC Cancer Protocol Summary for Treatment for Locally Advanced or Metastatic Medullary Thyroid Cancer Using vanDETanib. Vancouver, British Columbia: BC Cancer; 1 December 2018.