VENTURA COUNTY
HEALTH CARE PLAN

Prior Authorization DRUG Guidelines

Vandetanib (Brand Name: Caprelsa®)

Effective Date: 1/31/12

Date Developed: 12/14/11 by Albert Reeves MD

Last Approval Date: 1/26/16, 1/24/17, 1/23/18, 1/22/19, 2/18/20

Vandetanib is an Antineoplastic Agent, Tyrosine Kinase Inhibitor; Epidermal Growth Factor Receptor (EGFR) Inhibitor; Vascular Endothelial Growth Factor (VEGF) Inhibitor.

Pre-Authorization Criteria:
VCHCP will authorize Vandetanib (Brand Name: Caprelsa) for FDA approved indication for treatment of metastatic or unresectable locally advanced medullary thyroid cancer (symptomatic or progressive).
VCHCP requires that Vandetanib be prescribed by an Oncologist and Endocrinologist.

Dosing: Adult
Note: Do not initiate treatment unless QTcF <450 msec. Avoid concomitant use of QT-prolonging agents and strong CYP3A4 inducers. To reduce the risk of QT prolongation, maintain serum calcium and magnesium within normal limits and maintain serum potassium ≥4 mEq/L.

Medullary thyroid cancer, locally advanced or metastatic: Oral: 300 mg once daily, continue treatment until no longer clinically benefiting or until unacceptable toxicity.

Dosing: Geriatric
Refer to adult dosing.

Dosage Forms: U.S.
Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, oral: 100 mg, 300 mg

Caprelsa®: 100 mg, 300 mg

Administration

May be administered with or without food. Missed doses should be omitted if within 12 hours of the next scheduled dose. Do not crush tablet. If unable to swallow tablet whole or if nasogastric or gastrostomy tube administration is necessary, disperse one tablet in 2 ounces of water (noncarbonated only) and stir for 10 minutes to disperse (will not dissolve completely) and administer immediately. Rinse residue in glass with additional 4 ounces of water (noncarbonated only) and administer. Use appropriate handling precautions (hazardous agent).

Contraindications

Congenital long QT syndrome

WARNINGS / PRECAUTIONS

Concerns related to adverse effects:

Diarrhea: Diarrhea has been reported with use; may cause electrolyte imbalance (closely monitor electrolytes). Routine antidiarrheals are recommended. Withhold treatment until resolution for severe diarrhea; dose reduction is recommended when treatment is resumed.

Heart failure: Heart failure (HF) has been reported; monitor for signs and symptoms of HF. May require discontinuation. HF may not be reversible upon discontinuation.

Hemorrhage: Serious and sometimes fatal hemorrhagic events have been reported with use. Discontinue in patients with severe hemorrhage. Do not administer in patients with a recent history of hemoptysis with ≥2.5 mL of red blood.

Hypertension: Hypertension and hypertensive crisis have been observed with vandetanib. Monitor blood pressure and initiate or adjust antihypertensive therapy as needed. May require vandetanib dosage adjustment or treatment interruption; discontinue vandetanib (permanently) if blood pressure cannot be adequately controlled.

Hypothyroidism: Increased doses of thyroid replacement therapy have been required in patients with prior thyroidectomy. Obtain TSH at baseline, at 2-4 weeks, 8-12 weeks and every 3 months after vandetanib initiation. If signs and symptoms of hypothyroidism occur during treatment, evaluate thyroid hormone levels and adjust replacement therapy if needed.

Ischemic events: Ischemic cerebrovascular events (some fatal) have been observed with vandetanib. Discontinue treatment in patients with severe ischemic events. The safety of resuming treatment after an ischemic event has not been studied.

Pulmonary toxicity: Interstitial lung disease (ILD) or pneumonitis (including fatalities) has been reported with vandetanib. Patients should be advised to report any new or worsening respiratory symptoms; ILD should be suspected with nonspecific respiratory symptoms such as hypoxia, pleural effusion, cough or dyspnea. If asymptomatic (or minimal symptoms) although with radiologic evidence of ILD, may continue treatment with close monitoring; consider interrupting treatment for moderate symptoms (may require corticosteroids or antibiotics). Discontinue treatment for severe symptoms; may require corticosteroids and antibiotics, and permanent discontinuation.

QT prolongation/sudden death: **[U.S. Boxed Warning]: May prolong the QT interval; torsade de pointes and sudden death have been reported. Do not use in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Correct electrolyte imbalance prior to initiating therapy. Monitor electrolytes and ECG (to monitor QT interval) at baseline, at 2-4 weeks, at 8-12 weeks, and every 3 months thereafter; monitoring (at the same frequency) is required following dose reductions for QT prolongation or with dose interruptions >2 weeks. Avoid the use of QT-prolonging agents; if concomitant use with QT prolonging agents cannot be avoided, monitor ECG more frequently. Vandetanib has a long half-life (19 days), therefore, adverse reactions (including QT prolongation) may resolve slowly; monitor appropriately.** Ventricular tachycardia has also been reported. The potential for QT prolongation is dose dependent. Do not initiate treatment unless QT interval, Fridericia (QTcF) is <450 msec. During treatment, if QTcF >500 msec, withhold vandetanib and resume at a reduced dose when QTcF is <450 msec. Avoid use in patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure. Patients with ventricular arrhythmias or recent MI were excluded from clinical trials. To reduce the risk of QT prolongation, maintain serum calcium and magnesium within normal limits and maintain serum potassium ≥4 mEq/L.

Reversible posterior leukoencephalopathy syndrome (RPLS): RPLS been observed with vandetanib. Symptoms of RPLS include altered mental function, confusion, headache, seizure, or visual disturbances; generally associated with hypertension. Consider discontinuing treatment if RPLS occurs.

Skin reactions: Stevens-Johnson syndrome and other serious skin reactions (including fatal) have been reported. Mild-to-moderate skin reactions, including acne, dermatitis, dry skin, palmar-plantar erythrodysesthesia syndrome, pruritus, and rash have also been reported. Withhold treatment for dermatologic toxicity of grade 3 or higher; consider a reduced dose or permanent discontinuation upon improvement in symptoms. Severe dermatologic toxicity has been managed with corticosteroids (systemic) and treatment discontinuation; mild-to-moderate toxicity has responded to corticosteroids (systemic or topical), oral antihistamines, and antibiotics (topical or systemic). Increased risk of

photosensitivity is associated with vandetanib; effective sunscreen and protective clothing are recommended during and for at least 4 months after treatment discontinuation.

Disease-related concerns:

Hepatic impairment: Not recommended for use in patients with moderate to severe hepatic impairment.

Renal impairment: Dosage reduction is recommended in patients with moderate-to-severe renal impairment. Exposure is increased in patients with impaired renal function; closely monitor QT interval. Has not been studied in patients with end stage renal disease requiring dialysis.

DRUG Interactions

(For additional information: Launch Lexi-Interact™ Drug Interactions Program)

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Artemether: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Chloroquine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin (Systemic): May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Colchicine: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Colchicine. Colchicine distribution into certain tissues (e.g., brain) may also be increased. Management: Colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving a p-glycoprotein inhibitor. In those with normal renal and

hepatic function, reduce colchicine dose as directed. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Vandetanib. *Risk X: Avoid combination*

Dabigatran Etexilate: P-glycoprotein/ABCB1 Inhibitors may increase serum concentrations of the active metabolite(s) of Dabigatran Etexilate. Management: Dabigatran dose reductions may be needed. According to Canadian labeling, dabigatran dose for prevention of venous thromboembolism post hip or knee replacement should be reduced to 150 mg/day in patients receiving amiodarone, verapamil, or quinidine. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dronedarone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Dronedarone. *Risk X: Avoid combination*

Everolimus: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Everolimus. Management: Everolimus dose reductions are required for patients being treated for subependymal giant cell astrocytoma or renal cell carcinoma. See prescribing information for specific dose adjustment and monitoring recommendations. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Lumefantrine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

P-glycoprotein/ABCB1 Substrates: May increase the serum concentration of P-glycoprotein/ABCB1 Inhibitors. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimozide: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Pimozide. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the arrhythmogenic effect of Vandetanib. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QUEtiapine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QuiNINE: QTc-Prolonging Agents may enhance the QTc-prolonging effect of QuiNINE. QuiNINE may enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Rivaroxaban: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Rivaroxaban. *Risk C: Monitor therapy*

Silodosin: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

St Johns Wort: May decrease the serum concentration of Vandetanib. *Risk X: Avoid combination*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Topotecan: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Topotecan: BCRP/ABCG2 Inhibitors may increase the serum concentration of Topotecan. *Risk D: Consider therapy modification*

Toremifene: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Toremifene. The risk for potentially dangerous arrhythmias may be increased. *Risk X: Avoid combination*

Vemurafenib: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Vemurafenib. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

REFERENCES

1. National Comprehensive Cancer Network® (NCCN), "Clinical Practice Guidelines in Oncology™: Thyroid Carcinoma," Version 1.2011. Available at http://www.nccn.org/professionals/physician_gls/PDF/thyroid.pdf

2. Robinson BG, Paz-Ares L, Krebs A, et al, "Vandetanib (100 mg) in Patients With Locally Advanced or Metastatic Hereditary Medullary Thyroid Cancer," *J Clin Endocrinol Metab*, 2010, 95(6):2664-71. [PubMed 20371662]

3. Wells SA Jr, Gosnell JE, Gagel RF, et al, "Vandetanib for the Treatment of Patients With Locally Advanced or Metastatic Hereditary Medullary Thyroid Cancer," *J Clin Oncol*, 2010, 28(5):767-72. [PubMed 20065189]

4. Wells SA, Robinson BG, Gagel RF, et al, "Vandetanib (VAN) in Locally Advanced or Metastatic Medullary Thyroid Cancer (MTC): A Randomized, Double-Blind Phase III Trial (ZETA)," *J Clin Oncol*, 2010, 28(15s):5503 [abstract 5503 from 2010 ASCO Annual Meeting].

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