

Appendix 3 *CAPRELSA REMS Prescriber Training Questions*

Prescriber Training Questions

The goal of the Prescriber Training Program is to help ensure that prescribers treating patients with **CAPRELSA**[®] (vandetanib) Tablets understand the risk for QT prolongation, Torsades de pointes and sudden death associated with CAPRELSA treatment. These are not the only risks associated with CAPRELSA. Please see the Prescribing Information for additional Warnings and Precautions and safety information on CAPRELSA.

Review each of the six sections and answer the question following each section. Select the one answer that is the best choice for each question. This 6-question assessment should take approximately 15 minutes to complete.

QT Prolongation, Torsades de pointes, and Sudden Death

- Torsades de pointes, ventricular tachycardia, and sudden deaths have occurred in patients treated with CAPRELSA® (vandetanib) Tablets
- CAPRELSA can prolong the QT interval in a concentration-dependent manner
 - In 231 medullary thyroid cancer patients randomized to receive CAPRELSA 300 mg once daily in the phase 3 clinical trial, CAPRELSA was associated with sustained plasma concentration-dependent QT prolongation.

	CAPRELSA 300 mg N=231		Placebo N=99	
	All Grades	Grade 3-4	All Grades	Grade 3-4
ECG QT Prolonged	14%	8%	1%	1%

- Among all patients who received CAPRELSA, 69% had QT prolongation >450 ms and 7% had QT prolongation >500 ms by ECG using Fridericia correction (QTcF)
- Based on the exposure-response relationship, among all patients who received CAPRELSA, the mean (90% CI) QTcF change from baseline (Δ QTcF) was 35 (33-36) ms for the 300-mg dose. The Δ QTcF remained above 30 ms for the duration of the trial (up to 2 years).
- 36% of patients who received CAPRELSA experienced greater than 60 ms increase in Δ QTcF
- Because of the 19-day half-life, adverse reactions including prolonged QT interval may not resolve quickly. Monitor appropriately

Q1. According to the Prescribing Information, QT prolongation, Torsades de pointes and sudden death have occurred in patients treated with CAPRELSA® (vandetanib) Tablets. CAPRELSA can prolong the QT interval in a concentration-dependent manner. Because of the 19-day half life, adverse reactions including prolonged QT interval may not resolve quickly

- a. All the above statements are True
 - b. All the above statements are False
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Patient Selection

CAPRELSA[®] (vandetanib) Tablets are approved for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

Use CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease only after careful consideration of the treatment related risks of CAPRELSA.

In addition when thinking about the risks of QT prolongation, Torsades de pointes and sudden death associated with CAPRELSA, consider the following when deciding if a patient is appropriate for CAPRELSA treatment:

- Do not use CAPRELSA in patients with
 - Congenital long QT syndrome
 - Torsades de pointes
 - Bradyarrhythmias or
 - Uncompensated heart failure
- Do not start CAPRELSA treatment in patients whose QTcF interval is greater than 450 ms
- CAPRELSA has not been studied in patients with ventricular arrhythmias or recent myocardial infarction
- Vandetanib exposure is increased in patients with impaired renal function defined as a creatinine clearance <50 mL/min

Please note that there are other considerations when deciding if CAPRELSA is the appropriate treatment. This material focuses on the risks of QT prolongation, Torsades de pointes, and sudden death associated with CAPRELSA. These are not the only risks associated with CAPRELSA. Please see the full Prescribing Information for CAPRELSA, including the boxed WARNING.

Q2. According to the Prescribing Information for CAPRELSA[®] (vandetanib) Tablets, which of the following statements is true?

- a. CAPRELSA is contraindicated in patients with congenital long QT syndrome
 - b. CAPRELSA should not be administered to patients with a history of Torsades de pointes, bradyarrhythmias, or uncompensated heart failure
 - c. CAPRELSA should not be started in patients with a QTcF interval greater than 450 ms
 - d. All the above
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ECG Monitoring

- Obtain an ECG:
 - At baseline
 - 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA[®] (vandetanib) Tablets and every 3 months thereafter
 - Following any dose reduction for QT prolongation or any dose interruptions >2 weeks (monitor as described above)
- Stop CAPRELSA in patients who develop a QTcF greater than 500 ms until the QTcF returns to less than 450 ms. CAPRELSA can then be resumed at a reduced dose
- Monitor ECGs more frequently in patients who experience diarrhea

Q3. According to the Prescribing Information, patients who develop a QTcF greater than 500 ms while on CAPRELSA[®] (vandetanib) Tablets treatment should:

- a. Continue CAPRELSA without interruption, at the current dose
 - b. Continue CAPRELSA without interruption, but at a reduced dose
 - c. Stop taking CAPRELSA until QTcF returns to less than 450 ms. Dosing of CAPRELSA can be resumed at a reduced dose.
 - d. None of the above
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Electrolyte Monitoring

- To help reduce the risk of QT prolongation:
 - Maintain serum potassium levels at ≥ 4 mEq/L (within normal range)
 - Maintain serum magnesium and calcium levels within normal ranges
- Obtain serum potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH):
 - At baseline
 - 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA[®] (vandetanib) Tablets and every 3 months thereafter
- Monitor electrolytes more frequently in patients who experience diarrhea. In the clinical trial, diarrhea occurred more frequently in patients treated with CAPRELSA compared to placebo

	CAPRELSA 300 mg N=231		Placebo N=99	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Diarrhea/colitis	57%	11%	27%	2%

Q4. According to the Prescribing Information, to help reduce the risk of electrocardiogram QT prolongation with CAPRELSA[®] (vandetanib) Tablets:

- a. Serum potassium levels should be maintained at 4mEq/L or higher (within normal range)
 - b. Serum magnesium levels should be maintained within normal range
 - c. Serum calcium levels should be maintained within normal range
 - d. All the above
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Drug Interactions

- Avoid the administration of CAPRELSA[®] (vandetanib) Tablets with agents that may prolong the QT interval or are associated with Torsades de pointes
 - These include antiarrhythmic drugs (including but not limited to amiodarone, disopyramide, procainamide, sotalol, dofetilide) and other drugs (including but not limited to chloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, pimozide)
 - For lists of other possible or conditional risk drugs, please visit the CredibleMeds[™] web site at www.azcert.org¹
- If drugs known to prolong the QT interval are given to patients already receiving CAPRELSA and no alternative therapy exists, perform ECG monitoring of the QT interval more frequently

References: 1. CredibleMeds[™]. QT drug lists by risk groups. <http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm>. Accessed June 15, 2016.

Q5. According to the Prescribing Information, administration of CAPRELSA[®] (vandetanib) Tablets should be avoided in patients who are also receiving other drugs which include:

- a. Drugs that may prolong QT interval
 - b. Anti-arrhythmic drugs
 - c. a and b
 - d. None of the above
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Dosing and Administration

- The recommended dose of CAPRELSA[®] (vandetanib) Tablets is 300 mg taken orally once daily until disease progression or unacceptable toxicity occurs
- The 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets) and then to 100 mg for CTCAE (Common Terminology Criteria for Adverse Events) grade 3 or greater toxicities
- Reduce the starting dose to 200 mg in patients with moderate (creatinine clearance ≥ 30 to < 50 mL/min) and severe (creatinine clearance < 30 mL/min) renal impairment
- CAPRELSA may be taken with or without food
- Do not take a missed dose within 12 hours of the next dose.
- CAPRELSA is available as 100 mg tablets and 300 mg tablets

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- Q6. According to the Prescribing Information, if a patient misses a dose of CAPRELSA[®] (vandetanib) Tablets:
- a. The missed dose should be taken by the patient at any time
 - b. The missed dose should not be taken by the patient if it is less than 12 hours before the next dose
 - c. The missed dose should be taken along with the next dose
 - d. None of the above
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