Appendix 2 *CAPRELSA REMS Prescriber Training Slide Deck*

Reference ID: 4098675

Prescriber Training Slide Deck

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CAPRELSA® (vandetinib) Tablets

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Caprelsa®
(vandetanib) Tablets

Introduction

- This presentation has been developed as part of the CAPRELSA REMS Program, a restricted distribution program, to mitigate the serious risks of QT prolongation, Torsades de pointes, and sudden death associated with use of CAPRELSA® (vandetanib) by:
  - Educating prescribers on the following:
    - Serious risks of QT prolongation, Torsades de pointes, and sudden death associated with use of CAPRELSA
    - The need to monitor for QT prolongation and electrolyte abnormalities
    - Appropriate management of QT prolongation to minimize the occurrence of Torsades de pointes and sudden death associated with use of CAPRELSA
  - Informing patients on the following:
    - Serious risks of QT prolongation, Torsades de pointes, and sudden death associated with use of CAPRELSA

Caprelsa®
(vandetanib) Tablets

Indication

CAPRELSA® (vandetanib) is a kinase inhibitor indicated 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.

Caprelsa®
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BOXED WARNING: QT Prolongation, Torsades de Points, and Sudden Death

WARNING: QT PROLONGATION, TORSADES DE POINTES, AND SUDDEN DEATH

- CAPRELSA® (vandetanib) Tablets can prolong the QT interval. Torsades de pointes and sudden death have occurred in patients receiving CAPRELSA.
- Do not use CAPRELSA in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Correct hypocalcemia, hypokalemia and/or hypomagnesemia prior to CAPRELSA administration. Monitor electrolytes periodically.
- Avoid drugs known to prolong the QT interval.
- Only prescribers and pharmacies certified with the restricted distribution program are able to prescribe and dispense CAPRELSA.

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Risk of QT Prolongation, Torsades de pointes, and Sudden Death

- QT prolongation, Torsades de pointes, ventricular tachycardia, and sudden deaths have occurred in patients receiving 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%

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Risk of QT Prolongation, Torsades de pointes, and Sudden Death *(continued)*

- In the phase 3 medullary thyroid cancer clinical trial:
  - Among all patients who received CAPRELSA® (vandetanib) Tablets, 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 (ΔQTcF) was 35 (33-36) ms for the 300-mg dose. The ΔQTcF 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 ΔQTcF
- Because of the 19-day half-life, adverse reactions including a prolonged QT interval may not resolve quickly. Monitor appropriately

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Patient Selection

- Do not use CAPRELSA® (vandetanib) 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 > 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

- This presentation 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

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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, conduct QT assessments as described above
- Stop CAPRELSA in patients who develop a QTcF > 500 ms until the QTcF returns to < 450 ms. Dosing of CAPRELSA can then be resumed at a reduced dose
- Monitor ECGs more frequently in patients who experience diarrhea

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Electrolyte Monitoring

- To help reduce the risk of QT prolongation:
  - Maintain serum potassium levels of ≥ 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® (vandetanib) Tablets 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%

Caprelsa®
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Drug Interactions

- Avoid administration of CAPRESLA® (vandetanib) Tablets with anti-arrhythmic drugs and other drugs known to prolong the QT interval
  - These include:
    - **Antiarrhythmic drugs:** Including but not limited to amiodarone, disopyramide, procainamide, sotalol, dofetilide
    - **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.org[1]
- If such drugs are given to patients already receiving CAPRELSA and no alternative therapy exists, perform ECG monitoring of the QT interval more frequently.

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

Caprelsa®
(vandetanib) Tablets

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 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

CTCAE=Common Terminology Criteria for Adverse Events

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Prescriber Certification in the CAPRELSA REMS Program

- **Only prescribers certified with the CAPRELSA REMS Program are able to prescribe CAPRELSA® (vandetanib) Tablets**
  - In order to prescribe CAPRELSA, you must:
    - **Step 1:** Review this *CAPRELSA REMS Prescriber Training Pamphlet or CAPRELSA REMS Prescriber Training Slide Deck* and the CAPRELSA Prescribing Information
    - **Step 2:** Begin enrollment in the CAPRELSA REMS Program by filling out the demographic information in the *CAPRELSA REMS Prescriber Enrollment Form* online or by calling the CAPRELSA REMS Program
    - **Step 3:** Continue with the enrollment process by completing the *CAPRELSA REMS Prescriber Training Questions* online or by calling the CAPRELSA REMS Program
    - **Step 4:** Complete the enrollment process by reviewing and acknowledging the prescriber agreement, including acknowledgement to review the *CAPRELSA Patient Brochure* with the patient or caregiver online or by calling the CAPRELSA REMS Program. At the completion of this process the prescriber is enrolled in the REMS and is considered certified to prescribe CAPRELSA

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Prescriber Responsibilities

After you enroll in the CAPRELSA REMS Program:

- Talk to your patients about the risks of QT prolongation, Torsades de pointes, and sudden death as well as the other risks associated with CAPRELSA® (vandetanib) treatment
- Review the CAPRELSA Patient Brochure with the patient or caregiver before starting treatment
- Monitor your patients as outlined in the Prescribing Information and this presentation
- Report any cases of QT prolongation, Torsades de pointes and/or sudden death to 1-800-745-4447

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Pharmacy Certification in the CAPRELSA REMS Program

- **Only pharmacies certified with the CAPRELSA REMS Program are able to dispense CAPRELSA® (vandetanib)**
  - CAPRELSA is available through Biologics Inc. Call 1-800-367-4999 or go to www.biologicstoday.com for more information
  - A prescription form is available at www.caprelsarems.com

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