Appendix 1 *CAPRELSA REMS Prescriber Training Pamphlet*

Reference ID: 4098675

Caprelsa®
(vandetanib) Tablets

REMS PROGRAM
RISK EVALUATION AND MITIGATION STRATEGY

CAPRELSA® (vandetanib) Tablets and Risk of QT Prolongation, Torsades de Pointes and Sudden Death

Prescriber Training Pamphlet

Reference ID: 4098675

Introduction

This training pamphlet has been developed as part of a REMS program to help educate healthcare providers on the **serious risks of QT prolongation, Torsades de pointes, and sudden death associated with use of CAPRELSA® (vandetanib) Tablets.**

Because of these serious risks, CAPRELSA is only available through the CAPRELSA Risk Evaluation and Mitigation Strategy (REMS) Program. Under the CAPRELSA REMS Program, **only certified prescribers and pharmacies** are able to prescribe and dispense CAPRELSA.

This pamphlet includes information about the serious risks associated with use of CAPRELSA, prescriber certification and enrollment, and how to help mitigate these serious risks through:

- Appropriate patient selection
- Electrocardiogram (ECG) monitoring
- Electrolyte monitoring
- Drug interaction awareness
- Appropriate dosing and administration

This pamphlet focuses on the serious risks of QT prolongation, Torsades de pointes, and sudden death associated with use of CAPRELSA. These are not the only risks associated with use of CAPRELSA. Please see the accompanying Prescribing Information for CAPRELSA, including the Boxed Warning.

Please see boxed WARNING on page 3 and accompanying Prescribing Information.

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Indication

CAPRELSA® (vandetanib) Tablets 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 progressive disease only after careful consideration of the treatment related risks of CAPRELSA.

Boxed WARNING

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

- **CAPRELSA 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.**

Caprelsa®
(vandetanib) Tablets

QT Prolongation, Torsades de Pointes, and Sudden Death

- QT Prolongation, 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 (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

Please see boxed WARNING on page 3 and accompanying Prescribing Information.

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:

Considerations for Patient Selection

- **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 Prescribing Information for CAPRELSA, including the boxed WARNING.

Caprelsa®
(vandetanib) Tablets

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

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 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%

Please see boxed WARNING on page 3 and accompanying Prescribing Information.

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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™ website at www.azcert.org[1]
- 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

Reference: 1. CredibleMeds™. QT drug lists by risk groups. http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm. Accessed April 26, 2016.

Dosing and Administration

- The recommended dose of CAPRELSA 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

Caprelsa®
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Prescriber Certification in the CAPRELSA® (vandetanib) Tablets REMS Program

Only prescribers certified with the CAPRELSA REMS Program are able to prescribe CAPRELSA

In order to prescribe CAPRELSA, you must:

Review the *CAPRELSA REMS Prescriber Training Pamphlet* or *CAPRELSA REMS Prescriber Training Slide Deck* and the Prescribing Information

Step 1

Begin enrollment in the CAPRELSA REMS Program by filling out the demographic information in the *CAPRELSA REMS Prescriber Enrollment Form* online or by calling

Step 2

Continue with the enrollment process by completing the *CAPRELSA REMS Prescriber Training Questions* online or by calling the CAPRELSA REMS Program

Step 3

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

Step 4

You are now ready to prescribe and to do so you can download the CAPRELSA Prescription Form at www.caprelsarems.com

To ENROLL, visit www.caprelsarems.com or call 1-800-817-2722.

Please see boxed WARNING on page 3 and accompanying Prescribing Information.

Prescriber Responsibilities

After you enroll in the CAPRELSA REMS Program, remember to:

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 treatment

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Review the CAPRELSA Patient Brochure with the patient or caregiver before starting treatment

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Monitor your patients as outlined in the Prescribing Information and this pamphlet

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Report any cases of QT prolongation, Torsades de pointes and/or sudden death to 1-800-745-4447

Pharmacy Certification

Only pharmacies certified with the CAPRELSA REMS Program are able to dispense CAPRELSA

- 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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