



REMS PROGRAM
RISK EVALUATION AND MITIGATION STRATEGY

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

Healthcare Provider Education Pamphlet

Important REMS Information for
Healthcare Providers

Introduction

CAPRELSA® (vandetanib) Tablets are approved by the United States Food and Drug Administration (FDA).

CAPRELSA 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 can prolong the QT interval and cases of Torsades de pointes and sudden death have occurred in patients receiving CAPRELSA.

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

About This Pamphlet

This pamphlet has been developed as part of a REMS to help educate healthcare providers on the serious risks of QT prolongation, Torsades de pointes, and sudden death associated with CAPRELSA.

The pamphlet includes information about these risks, about prescriber certification, and how to help mitigate these risks through:

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

This pamphlet 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 accompanying full Prescribing Information for CAPRELSA, including the boxed WARNING.

Please see boxed WARNING on page 10 and accompanying full Prescribing Information.

Prescriber and Pharmacy 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 this HCP Education pamphlet or
HCP REMS Education Slide Set; and the
CAPRELSA Full Prescribing Information**

Step 1



**Complete the Prescriber Training
Program (online or by phone)**

Step 2



**Complete the Prescriber
Enrollment Form**

Step 3

To ENROLL, visit www.caprelsarems.com or
call 1-800-236-9933.



After you enroll:

- 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® (vandetanib) Tablets treatment
- Review the Medication Guide with each patient or caregiver before starting treatment
- Monitor your patients as outlined in the full Prescribing Information and this pamphlet
- Report any cases of Torsades de pointes and sudden death to 1-800-236-9933

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

- CAPRELSA is available through Biologics Inc. Call 1-800-236-9933 or go to www.biologics.today.com for more information

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



Review the Medication Guide with the patient or caregiver before starting treatment



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



Report any cases of Torsades de pointes and sudden death to 1-800-236-9933

Please see boxed WARNING on page 10 and accompanying full Prescribing Information.

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 >60 ms increase in Δ QTcF
- Because of the 19-day half-life, adverse reactions including a prolonged QT interval may not resolve quickly. Monitor appropriately



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 >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 pamphlet 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 accompanying full Prescribing Information for CAPRELSA, including the boxed WARNING.

Please see boxed WARNING on page 10 and accompanying full Prescribing Information.

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 >500 ms until the QTcF is <450 ms. Dosing of CAPRELSA can then be resumed at a reduced dose
- Monitor ECGs more frequently in patients who experience diarrhea

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%

Recommendations for ECG Monitoring

- ECGs should be obtained:
 - 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 > 500 ms until QTcF is <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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- Monitor electrolytes more frequently in patients who experience diarrhea

Please see boxed **WARNING** on page 10 and accompanying full Prescribing Information.

Drug Interactions

- Avoid administration of CAPRELSA® (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) 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 such drugs 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 June 20, 2013.

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



**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.**

Please see accompanying full Prescribing Information for CAPRELSA.

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Caprelisa[®]
(vandetanib) Tablets

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