Initial REMS Approval: 04/2011

NDA 22-405
Caprelsa® (vandetanib)
Kinase inhibitor
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355
1-800-236-9933

RISK EVALUATION AND MITIGATION STRATEGY

I. GOALS

The goals of the CAPRELSA REMS are:

1. to educate prescribers about the risk, appropriate monitoring, and management of QT prolongation to help minimize the occurrence of Torsades de pointes and sudden death associated with CAPRELSA.

2. to inform patients about the serious risks associated with CAPRELSA.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each CAPRELSA prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the CAPRELSA REMS Program and is appended.

B. Communication Plan

AstraZeneca will implement a communication plan to healthcare providers to support implementation of this REMS.

The communication plan will include:

1. A *Dear Healthcare Provider (HCP) Letter* to be distributed at least 1 week prior to first availability of CAPRELSA to healthcare providers. The target audience will include medical oncologists, endocrinologists, and surgeons. This letter is designed to convey the risk and the need to complete training to become certified in order to

prescribe Caprelsa® (vandetanib). The letter will be accompanied by the Full Prescribing Information, Medication Guide, and prescriber education materials (outlined in Section C1(d) below). The letter will be available on the CAPRELSA REMS Program Web Site (www.caprelsarems.com) for 1 year from the date of distribution.

The *Dear Healthcare Provider Letter* is part of the CAPRELSA REMS Program and is appended.

2. AstraZeneca will communicate via a *Dear Professional Society Letter* to the leadership of the following professional societies and request that these societies disseminate this information to their members:
   - American Society of Clinical Oncology (ASCO)
   - American Thyroid Association (ATA)
   - National Comprehensive Cancer Network (NCCN)
   - Oncology Nursing Society (ONS)

   The letter will be accompanied by the full Prescribing Information (including the Medication Guide), and program materials (outlined in Section C1(d) below). The letter will be available on the CAPRELSA REMS Program website (www.caprelsarems.com) for 1 year from the date of distribution.

   If AstraZeneca has a presence at the above mentioned conferences where commercial CAPRELSA product information is displayed, AstraZeneca will display the CAPRELSA *REMS Convention Panel* outlining details of the CAPRELSA REMS Program.

   The *Dear Professional Society Letter* and CAPRELSA *REMS Convention Panel* are part of the CAPRELSA REMS Program and are appended.

C. Elements to Assure Safe Use

1. Healthcare providers who prescribe CAPRELSA are specially certified.

a. AstraZeneca will ensure that healthcare providers who prescribe CAPRELSA are specially certified.

b. To become certified to prescribe CAPRELSA, prescribers will be required to enroll in the CAPRELSA REMS Program and must:

   1) Review the CAPRELSA *REMS HCP Education Pamphlet* or *Slide Set* and the Full Prescribing Information which includes the Medication Guide.

   2) Complete the *Prescriber Training*.

3) Complete and sign the *CAPRELSA Prescriber Enrollment Form* and submit it to the CAPRELSA REMS Program.

4) Agree to review the *Medication Guide* with the patient or caregiver.

c. Prescribers are required to be re-trained following substantive changes to the CAPRELSA REMS. Substantive changes are defined as 1) significant changes to the operation of the CAPRELSA REMS Program; 2) changes to the Prescribing Information and Medication Guide that affect the risk benefit profile of Caprelsa® (vandetanib).

d. AstraZeneca will:

1) Ensure that prescriber enrollment can successfully be completed via the CAPRELSA *REMS website*, or by phone via the call center.

The CAPRELSA *REMS Web Site* (www.caprelsarems.com) is part of the CAPRELSA REMS Program and is appended.

2) Ensure that, as part of the enrollment process, prescribers receive or have access to the following materials that are part of the CAPRELSA REMS Program and are appended:

HCP Education Pamphlet
HCP Education slides set
Prescriber Training Program
Prescriber Enrollment form
Medication Guide

These materials will be sent promptly to any uncertified prescriber who attempts to prescribe CAPRELSA.

3) Ensure that prescribers have completed the training and ensure that the enrollment form is complete before activating a prescriber's enrollment in the CAPRELSA REMS Program.
4) Ensure that prescribers are notified when they are successfully enrolled in the CAPRELSA REMS Program, and therefore, are certified to prescribe CAPRELSA.

2. CAPRELSA will only be dispensed by pharmacies that are specially certified.

a. AstraZeneca will ensure that CAPRELSA will only be dispensed by certified pharmacies. To become certified to dispense CAPRELSA, each pharmacy must be enrolled in the CAPRELSA REMS Program.

b. To become certified, the authorized pharmacist on behalf of the pharmacy must agree to the following:

1) I understand that only prescribers enrolled in the CAPRELSA REMS Program can prescribe Caprelsa® (vandetanib).

2) The pharmacy must have a system in place to verify that the prescriber is enrolled in the CAPRELSA REMS Program each time CAPRELSA is dispensed. If the prescriber is not enrolled, CAPRELSA cannot be dispensed.

3) All pharmacy staff and critical employees involved in the dispensing of CAPRELSA will be educated on the risks and requirements of the CAPRELSA REMS Program.

4) The pharmacy will provide the Medication Guide each time CAPRELSA is dispensed.

5) The pharmacy will ensure that it has adequate processes and procedures in place and that those processes and procedures are being followed for the CAPRELSA REMS Program.

6) The pharmacy will maintain a system, records and documentation that can be audited to document compliance with the CAPRELSA REMS Program; including prescriber certification each time CAPRELSA is dispensed.

7) Complete and sign the *CAPRELSA Pharmacy Enrollment Form* and submit it to the CAPRELSA REMS Program.

The *CAPRELSA Pharmacy Enrollment Form* is part of the REMS and is appended.

D Implementation System

1. AstraZeneca will ensure that pharmacies (including pharmacy distributors) dispensing CAPRELSA are specially certified using the criteria described above.

2. AstraZeneca will ensure that distributors who distribute CAPRELSA are specially certified. Specially certified distributors will agree to:

a. Distribute CAPRELSA only to pharmacies certified in the CAPRELSA REMS.

b. Put processes and procedures in place to ensure that the requirements of the CAPRELSA REMS are followed.

c. Agree to be audited to ensure that CAPRELSA is distributed according to the REMS.

3. AstraZeneca will maintain a secure, validated, interactive, web-based database of all enrolled entities (prescribers, pharmacies, and distributors). Prescribers will be able to enroll in the program by completing the enrollment requirements online. Certified pharmacies can access the database to verify prescriber enrollment status as required by the REMS.

4. AstraZeneca will monitor distribution and prescription data to ensure that only enrolled distributors are distributing, enrolled pharmacies are dispensing, and enrolled prescribers are prescribing Caprelsa® (vandetanib). Corrective action will be initiated by AstraZeneca for prescribers, pharmacies, or distributors who are found not to be complying with the REMS.

    a. Inpatients in acute care settings will be shipped drug per patient if the prescriber is enrolled in the REMS

    b. Patients in long-term care facilities will be shipped drug per patient if the prescriber is enrolled in the REMS

    c. All shipments of CAPRELSA will be accompanied by a Medication Guide.

5. AstraZeneca will monitor and audit the online enrollment database, distribution, and dispensing systems to check that all processes and procedures are in place and functioning to support the requirements of the CAPRELSA REMS Program.

6. AstraZeneca will maintain a Program Coordinating Center with a Call Center to support patients, prescribers, pharmacies, and distributors in interfacing with the REMS. AstraZeneca will ensure that all materials listed in or appended to the CAPRELSA REMS Program will be available through the REMS website (www.caprelsarems.com) or by calling the Call Center at 1-800-236-9933.

7. If there are substantive changes to the CAPRELSA REMS Program, AstraZeneca will update all affected materials and notify pharmacies, prescribers, and distributors, as applicable. Substantive changes are defined as:

    a. Significant changes to the operation of the CAPRELSA REMS Program

    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of CAPRELSA.

8. Based on monitoring and evaluation of these elements to assure safe use, AstraZeneca will take reasonable steps to improve implementation of these elements and to maintain compliance with the CAPRELSA REMS Program requirements, as applicable.

9. AstraZeneca will develop, train appropriate personnel, and follow written procedures and scripts to implement the REMS program. AstraZeneca will modify them as required based on the results of assessments.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

AstraZeneca will submit assessments of the Caprelsa® (vandetanib) REMS Program to the FDA every 6 months for the first year following the approval of the CAPRELSA REMS, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date of the assessment. AstraZeneca will submit each assessment so that it will be received by the FDA on or before the due date.

AstraZeneca

IMPORTANT DRUG WARNING

SUBJECT: Serious Risks of QT prolongation, Torsades de pointes and Sudden death for Caprelsa® (vandetanib); FDA required restricted distribution program.

DATE

Dear Healthcare Provider:

AstraZeneca Pharmaceuticals LP would like to inform you of the approval of CAPRELSA (vandetanib), a new kinase inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of CAPRELSA.

CAPRELSA can prolong the QT interval and cases of Torsades de pointes and sudden death were reported in clinical trials. Because of these risks, CAPRELSA is available only through a restricted distribution program called CAPRELSA REMS Program. **Under the CAPRELSA REMS Program, only prescribers and pharmacies enrolled in the program can prescribe and dispense CAPRELSA.**

In order to prescribe CAPRELSA, you must:

- Read this Healthcare Provider (HCP) Letter; review HCP Education Pamphlet or HCP REMS Education Slide Set; and the CAPRELSA full Prescribing Information
- Complete the Prescriber Training Program (online or by phone)
- Complete the Prescriber Enrollment Form

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

Please see the enclosed **HCP Education Pamphlet** that outlines the risk of QT prolongation, Torsades de pointes and sudden death associated with CAPRELSA.

This is not a complete list of all the Warnings and Precautions of CAPRELSA. Please see the enclosed full Prescribing Information for CAPRELSA.

Sincerely,

James W. Blasetto, M.D., MPH
Vice President, US Strategic Development
AstraZeneca LP
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

1181800 4/11

AstraZeneca

IMPORTANT DRUG WARNING

SUBJECT: **Serious Risks of QT prolongation, Torsades de pointes and Sudden death for Caprelsa® (vandetanib); FDA required restricted distribution program.**

DATE

Dear (Medical Society):

AstraZeneca Pharmaceuticals LP would like to inform you and your membership of the approval of CAPRELSA (vandetanib), a new kinase inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of CAPRELSA.

CAPRELSA can prolong the QT interval and cases of Torsades de pointes and sudden death were reported in clinical trials. Because of these risks, CAPRELSA is available only through a restricted distribution program called CAPRELSA REMS Program. **Under the CAPRELSA REMS Program, only prescribers and pharmacies enrolled in the program can prescribe and dispense CAPRELSA.**

In order to prescribe CAPRELSA, prescribers must:

- Read the Healthcare Provider (HCP) Letter; review HCP Education Pamphlet or HCP REMS Education Slide Set; and the CAPRELSA full Prescribing Information
- Complete the Prescriber Training Program (online or by phone)
- Complete the Prescriber Enrollment Form

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

To increase awareness of QT prolongation, Torsades de pointes and sudden death and the requirement for prescribers to enroll, please share this communication with the members of your society. We would ask that you also provide a link to the CAPRELSA REMS website at www.CAPRELSArems.com when disseminating this information to your members.

Please see the enclosed **HCP Education Pamphlet** that outlines the risk of QT prolongation, Torsades de pointes and sudden death associated with CAPRELSA.

This is not a complete list of all the Warnings and Precautions of CAPRELSA. Please see the enclosed full Prescribing Information for CAPRELSA.

Sincerely,

James W. Blasetto, M.D., MPH
Vice President, US Strategic Development
AstraZeneca LP
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Caprelsa® (vandetanib)

REMS PROGRAM

RISK EVALUATION AND MITIGATION STRATEGY

Important Information for Healthcare Providers About the Risk of QT Prolongation, Torsades de Pointes, and Sudden Death With CAPRELSA (vandetanib) Tablets

CAPRELSA can prolong the QT interval and cases of Torsades de pointes and sudden death were reported in clinical trials. Because of this risk, CAPRELSA is only available through the CAPRELSA Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program. Under the CAPRELSA REMS Program, **only prescribers and pharmacies enrolled in the program can prescribe and dispense CAPRELSA.**

In order to prescribe CAPRELSA, a physician must:

- Review the educational materials, including:
  - Risk information regarding QT prolongation, Torsades de pointes, and sudden death with CAPRELSA
  - Considerations for patient selection
  - ECG and electrolyte monitoring requirements
  - Drug interaction information
  - Dosage and administration information
- Complete the Prescriber Training Program
- Complete the Prescriber Enrollment Form

CAPRELSA is a kinase inhibitor that has been approved by the United States Food and Drug Administration for:

Treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

Use of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of CAPRELSA.

To learn more about the specific REMS requirements and to ENROLL in the CAPRELSA REMS Program call 1-800-236-9933 or visit www.caprelsarems.com

The CAPRELSA REMS Program Prescriber Enrollment Form

A prescriber must enroll in the CAPRELSA REMS Program to prescribe Caprelsa® (vandetanib). Please complete the information below and then continue with certification by clicking the NEXT button on your screen

Prescriber Information

First Name: _____Middle Initial: _____Last Name: _____

Credentials: □ MD □ DO □ NP □ PA □ Other

Physician Specialty: □ Medical Oncologist □ Endocrinologist □ Surgeon □ Other_____

Name of Facility: _____

Address 1: _____

Address 2: _____

City: _____ State: _____ Zip code: _____

Phone Number: _____Fax Number: _____

Email: _____

State License Number: _____ State of Issue: _____

National Provider Identification (NPI) Number: _____

Prescriber Agreement

I understand that CAPRELSA is only available through the CAPRELSA REMS Program and I must comply with the program requirements. In addition, I acknowledge that:

1. I have read the HCP Educational Pamphlet or the HCP REMS Education Slide Set, and the Full Prescribing Information for CAPRELSA, including the Medication Guide, and I have completed the prescriber training program.
2. I understand that CAPRELSA is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of CAPRELSA.
3. **Risk of QT prolongation, Torsades de pointes, and Sudden Death**
   a. I understand that CAPRELSA can prolong the QT interval in a concentration-dependent manner, and that Torsades de pointes and sudden death have been reported in patients administered CAPRELSA.
   b. I understand that a prolonged QT interval may NOT resolve quickly because of the 19-day half-life.

c. I understand that CAPRELSA must not be administered to patients with congenital long QT syndrome.
d. I will report cases of Torsades de pointes and sudden death to AstraZeneca.

4. **QT Monitoring – I understand that**
   a. ECGs should be obtained to monitor the QT at **baseline**, **at 2-4 weeks** and **8-12 weeks after starting treatment** with CAPRELSA **and every 3 months** thereafter.
   b. Patients who develop a QTcF greater than 500 ms should stop taking CAPRELSA until QTcF returns to less than 450 ms. Dosing of CAPRELSA can be resumed at a reduced dose.
   c. Following any dose reduction for QT prolongation, or any dose interruptions greater than 2 weeks, QT assessment should be conducted as described above.

5. **Electrolyte Monitoring – I understand that**
   a. CAPRELSA should not be used in patients with hypocalcemia, hypokalemia, and/or hypomagnesemia.
   b. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to CAPRELSA administration and should be periodically monitored.
   c. Electrolytes may require more frequent monitoring in case of diarrhea.

6. **Drug Interactions – I understand that**
   a. Drugs known to prolong the QT interval should be avoided.
   b. If the patient must take a drug known to prolong the QT interval; I need to monitor the QT interval more frequently and adjust the dose of CAPRELSA.

7. **Dosing – I understand**
   a. The exposure to CAPRELSA is increased in patients with impaired renal function. The starting dose should be reduced to 200 mg in patients with moderate to severe renal impairment and QT interval should be monitored closely.
   b. How to properly dose and administer CAPRELSA.

8. I will review and counsel each patient or caregiver on the CAPRELSA Medication Guide and the risks and benefits of CAPRELSA.
9. I understand that CAPRELSA will only be available through pharmacies enrolled in the CAPRELSA REMS Program.
10. I understand that CAPRELSA is only available through the CAPRELSA REMS Program. I understand and agree to comply with the CAPRELSA REMS Program requirements for prescribers.

Prescriber Signature: _____ Date: _____

Caprelsa®
(vandetanib)

REMS PROGRAM
RISK EVALUATION AND MITIGATION STRATEGY

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

Healthcare Provider Education Pamphlet

Important REMS Information for Healthcare Providers

Reference ID: 2964738

Introduction

CAPRELSA (vandetanib), a kinase inhibitor, has been approved by the United States Food and Drug Administration (FDA).

CAPRELSA is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

Use of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of CAPRELSA.

CAPRELSA can prolong the QT interval and cases of Torsades de pointes and sudden death were reported in clinical trials. Because of this risk, CAPRELSA is only available through the CAPRELSA Risk Evaluation and Mitigation Strategy (REMS) Program. Under the CAPRELSA REMS Program, only prescribers and pharmacies enrolled in the restricted distribution program can 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) REMS Program

Only prescribers enrolled in the CAPRELSA REMS Program can prescribe CAPRELSA

In order to prescribe CAPRELSA, you must:

Read the Dear Healthcare Provider (HCP) Letter; 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.

Caprelsa® (vandetanib) Tablets

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) treatment
- Review the Medication Guide with each patient 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 enrolled in the CAPRELSA REMS Program can dispense CAPRELSA

- CAPRELSA is available through Biologics Inc. Call 1-800-236-9933 or go to www.biologicstoday.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

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

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

QT Prolongation, Torsades de Pointes, and Sudden Death

- Torsades de pointes, ventricular tachycardia, and sudden deaths have been reported in patients administered CAPRELSA (vandetanib)
  - In the phase 3 medullary thyroid cancer clinical trial, there was one sudden death and one death from cardiopulmonary arrest in patients receiving CAPRELSA after data cut-off
- 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	33 (14%)	18 (8%)	1 (1%)	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 >60 ms increase in ΔQTcF
  - CAPRELSA has a half-life of 19 days, adverse reactions including prolonged QT interval may not resolve quickly. Monitor appropriately

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

Caprelsa® (vandetanib) Tablets

Patient Selection

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

Use of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because 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**
- **CAPRELSA treatment should not be started in patients whose QTcF interval is >450 ms**
- **CAPRELSA should not be given to patients who have a history of:**
  - **Torsades de pointes**
  - **Bradyarrhythmias or**
  - **Uncompensated heart failure**
- **CAPRELSA has not been studied in patients with ventricular arrhythmias or recent myocardial infarction**
- **CAPRELSA 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.

ECG Monitoring

- ECGs should be obtained:
  - At baseline
  - 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA (vandetanib) and every 3 months thereafter
  - Following any dose reduction for QT prolongation or any dose interruptions >2 weeks (monitor as described above)
- Patients who develop QTcF >500 ms should stop taking CAPRELSA until QTcF is <450 ms. CAPRELSA can be resumed at a reduced dose
- ECGs may require more frequent monitoring in cases of diarrhea

Electrolyte Monitoring

- To help reduce the risk of QT prolongation:
  - Serum potassium levels should be maintained at ≥4 mEq/L (within normal range)
  - Serum magnesium and calcium levels should be kept within normal range
- Levels of serum potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH) should be obtained:
  - At baseline
  - 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA and every 3 months thereafter
- Electrolytes may require more frequent monitoring in cases of 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	132 (57%)	26 (11%)	27 (27%)	2 (2%)

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

Caprelsa® (vandetanib) Tablets

Recommendations for ECG Monitoring

- **ECGs should be obtained:**
  - **At baseline**
  - **2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA (vandetanib) and every 3 months thereafter**
  - **Following any dose reduction for QT prolongation or any dose interruptions >2 weeks (monitor as described above)**
- **Patients who develop QTcF >500 ms should stop taking CAPRELSA until QTcF is <450 ms. CAPRELSA can be resumed at a reduced dose**
- **ECGs may require more frequent monitoring in cases of diarrhea**

Recommendations for Electrolyte Monitoring

- **To help reduce the risk of QT prolongation:**
  - **Serum potassium levels should be maintained at ≥4 mEq/L (within normal range)**
  - **Serum magnesium and calcium levels should be kept within normal range**
- **Levels of serum potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH) should be obtained:**
  - **At baseline**
  - **2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA and every 3 months thereafter**
- **Electrolytes may require more frequent monitoring in cases of diarrhea**

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

Drug Interactions

- Drugs that prolong the QT interval or are associated with Torsades de pointes should be avoided in combination with CAPRELSA (vandetanib)
  - 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 Arizona CERT Web site at www.azcert.org[1]
- If no alternative therapy exists and concomitant treatment with a drug that is known to prolong the QT interval is medically necessary, ECG monitoring of the QT interval should be performed more frequently

Reference: 1. Arizona Center for Education and Research on Therapeutics (CERT). QT drug lists by risk groups. http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm. Accessed March 21, 2011.

Dosing and Administration

- The recommended daily dose is 300 mg of CAPRELSA taken orally, continued until patients are no longer benefiting from treatment or an unacceptable toxicity occurs
- The 300 mg daily dose may be reduced to 200 mg (two 100 mg tablets) and then to 100 mg based on CTCAE (Common Terminology Criteria for Adverse Events) grade 3 or greater toxicities
- The starting dose should be reduced to 200 mg in patients with moderate (creatinine clearance ≥30 to <50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment. QT interval should be monitored closely
- CAPRELSA may be taken with or without food
- If a patient misses a dose of CAPRELSA, the missed dose should not be taken if it is less than 12 hours before the next dose
- CAPRELSA is available as 100 mg tablets and 300 mg tablets

Caprelsa® (vandetanib) Tablets

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

- **CAPRELSA (vandetanib) can prolong the QT interval. Torsades de pointes and sudden death have been reported in patients receiving CAPRELSA.**
- **CAPRELSA should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to CAPRELSA administration and should be periodically monitored.**
- **Drugs known to prolong the QT interval should be avoided. If a drug known to prolong the QT interval must be administered, more frequent ECG monitoring is recommended.**
- **Given the half-life of 19 days, ECGs should be obtained to monitor the QT at baseline, at 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA and every 3 months thereafter. Following any dose reduction for QT prolongation, or any dose interruptions greater than 2 weeks, QT assessment should be conducted as described above.**
- **Because of the 19-day half-life, adverse reactions including a prolonged QT interval may not resolve quickly. Monitor appropriately.**
- **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.

Caprelsa® (vandetanib) Tablets

1181803 4/11 Printed in USA

Caprelsa® (vandetanib); and Risk of QT Prolongation, Torsades de Pointes and Sudden Death

Healthcare Provider Risk Evaluation and Mitigation Strategy (REMS) Education Slide Set

Important REMS Information for Healthcare Providers

Caprelsa® (vandetanib) Tablets

Introduction

- This presentation has been developed as part of the CAPRELSA REMS Program, a restricted distribution program, to help educate healthcare providers on the serious risks of QT prolongation, Torsades de pointes, and sudden death associated with CAPRELSA (vandetanib)
- 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 of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of CAPRELSA
- This presentation 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 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

Caprelsa® (vandetanib) Tablets

Prescriber and Pharmacy Certification in the CAPRELSA REMS Program

- **Only prescribers enrolled in the CAPRELSA REMS Program can prescribe CAPRELSA (vandetanib)**
  - In order to prescribe CAPRELSA, you must:
    - Read the Dear Healthcare Provider (HCP) Letter; review this HCP REMS Education Slide Set or HCP Education pamphlet; and the CAPRELSA full Prescribing Information
    - Complete the Prescriber Training Program (online or by phone)
    - Complete the Prescriber Enrollment Form
  - 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 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 presentation
    - Report any cases of Torsades de pointes and sudden death to 1-800-236-9933
- **Only pharmacies enrolled in the CAPRELSA REMS Program can dispense CAPRELSA**
  - CAPRELSA is available through Biologics Inc. Call 1-800-236-9933 or go to www.biologicstoday.com for more information

Caprelsa® (vandetanib) Tablets

QT Prolongation, Torsades de pointes, and Sudden Death

- Torsades de pointes, ventricular tachycardia, and sudden deaths have been reported in patients administered CAPRELSA (vandetanib)
  - In the phase 3 medullary thyroid cancer clinical trial, there was one sudden death and one death from cardiopulmonary arrest in patients receiving CAPRELSA after data cut-off
- 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	33 (14%)	18 (8%)	1 (1%)	1 (1%)

Caprelsa® (vandetanib) Tablets

Reference ID: 2964738

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), 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
- CAPRELSA has a half-life of 19 days, adverse reactions including prolonged QT interval may not resolve quickly. Monitor appropriately

Caprelsa® (vandetanib) Tablets

Patient Selection

- In addition to thinking about the risks of QT prolongation, Torsades de pointes and sudden death associated with CAPRELSA (vandetanib), consider the following when deciding if a patient is appropriate for CAPRELSA treatment:
  - Do not use CAPRELSA in patients with congenital long QT syndrome
  - CAPRELSA treatment should not be started in patients whose QTcF interval is >450 ms
  - CAPRELSA should not be given to patients who have a history of
    - Torsades de pointes
    - bradyarrhythmias or
    - uncompensated heart failure
  - CAPRELSA has not been studied in patients with ventricular arrhythmias or recent myocardial infarction
  - CAPRELSA 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

Caprelsa® (vandetanib) Tablets

ECG Monitoring

- ECGs should be obtained:
  - At baseline
  - 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA (vandetanib) and every 3 months thereafter
  - Following any dose reduction for QT prolongation or any dose interruptions >2 weeks (monitor as described above)
- Patients who develop QTcF >500 ms should stop taking CAPRELSA until QTcF is <450 ms. CAPRELSA can be resumed at a reduced dose
- ECGs may require more frequent monitoring in cases of diarrhea

Caprelsa® (vandetanib) Tablets

Electrolyte Monitoring

- To help reduce the risk of QT prolongation:
  - Serum potassium levels should be maintained at ≥4 mEq/L (within normal range)
  - Serum magnesium and calcium levels should be kept within normal range
- Levels of serum potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH) should be obtained:
  - At baseline
  - 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA (vandetanib) and every 3 months thereafter
- Electrolytes may require more frequent monitoring in cases of 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	132 (57%)	26 (11%)	27 (27%)	2 (2%)

Caprelsa® (vandetanib) Tablets

Reference ID: 2964738

Drug Interactions

- Drugs that prolong the QT interval or are associated with Torsades de pointes should be avoided in combination with CAPRELSA (vandetanib)
  - 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 Arizona CERT Web site at www.azcert.org[1]
- If no alternative therapy exists and concomitant treatment with a drug that is known to prolong the QT interval is medically necessary, ECG monitoring of the QT interval should be performed more frequently

1. Arizona Center for Education and Research on Therapeutics (CERT). QT drug lists by risk groups. http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm. Accessed March 21, 2011.

Caprelsa® (vandetanib) Tablets

Dosing and Administration

- The recommended daily dose is 300 mg of CAPRELSA (vandetanib) taken orally, continued until patients are no longer benefiting from treatment or an unacceptable toxicity occurs
- The 300 mg daily dose may be reduced to 200 mg (two 100 mg tablets) and then to 100 mg based on CTCAE grade 3 or greater toxicities
- The starting dose should be reduced to 200 mg in patients with moderate (creatinine clearance ≥30 to <50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment. QT interval should be monitored closely
- CAPRELSA may be taken with or without food
- If a patient misses a dose of CAPRELSA, the missed dose should not be taken if it is less than 12 hours before the next dose
- CAPRELSA is available as 100 mg tablets and 300 mg tablets

CTCAE=Common Terminology Criteria for Adverse Events

Caprelsa® (vandetanib) Tablets

WARNING: QT Prolongation, Torsades de Points, and Sudden Death

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

- **CAPRELSA (vandetanib) can prolong the QT interval. Torsades de pointes and sudden death have been reported in patients receiving CAPRELSA.**
- **CAPRELSA should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to CAPRELSA administration and should be periodically monitored.**
- **Drugs known to prolong the QT interval should be avoided. If a drug known to prolong the QT interval must be administered, more frequent ECG monitoring is recommended.**
- **Given the half-life of 19 days, ECGs should be obtained to monitor the QT at baseline, at 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA and every 3 months thereafter. Following any dose reduction for QT prolongation, or any dose interruptions greater than 2 weeks, QT assessment should be conducted as described above.**
- **Because of the 19-day half-life, adverse reactions including a prolonged QT interval may not resolve quickly. Monitor appropriately.**
- **Only prescribers and pharmacies certified with the restricted distribution program are able to prescribe and dispense CAPRELSA.**

Caprelsa® (vandetanib) Tablets

CAPRELSA REMS Web Site

Caprelsa® (vandetanib) REMS PROGRAM
RISK EVALUATION AND MITIGATION STRATEGY

Search Go

For US audiences only

AstraZeneca

Prescribing CAPRELSA

- Important Safety Information Including Boxed WARNING
- Approved Indication
- Full Prescribing Information for CAPRELSA
- Medication Guide for CAPRELSA
- CAPRELSA Prescription Form

REMS Home

- Educational Materials
- Learn About the CAPRELSA REMS Program
- Enroll Into the CAPRELSA REMS Program
- Contact Us

Welcome to the CAPRELSA REMS Program

CAPRELSA (vandetanib) Tablets, a kinase inhibitor, is approved by the Food and Drug Administration (FDA) for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of CAPRELSA.

CAPRELSA can prolong the QT interval and cases of Torsades de pointes and sudden death were reported in clinical trials. Because of this risk, CAPRELSA is only available through the CAPRELSA Risk Evaluation and Mitigation Strategy (REMS) Program.

The CAPRELSA REMS Program has the following specific goals:

- To educate prescribers about the risk, appropriate monitoring, and management of QT prolongation to help minimize the occurrence of Torsades de pointes and sudden death
- To inform patients about the serious risks associated with CAPRELSA

Under the CAPRELSA REMS Program, only certified prescribers can prescribe CAPRELSA.

CAPRELSA REMS Program: Learn and Enroll

Learn About the CAPRELSA REMS Program

Enroll Into the CAPRELSA REMS Program

Indication

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 of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of CAPRELSA.

Important Safety Information, including boxed WARNING

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

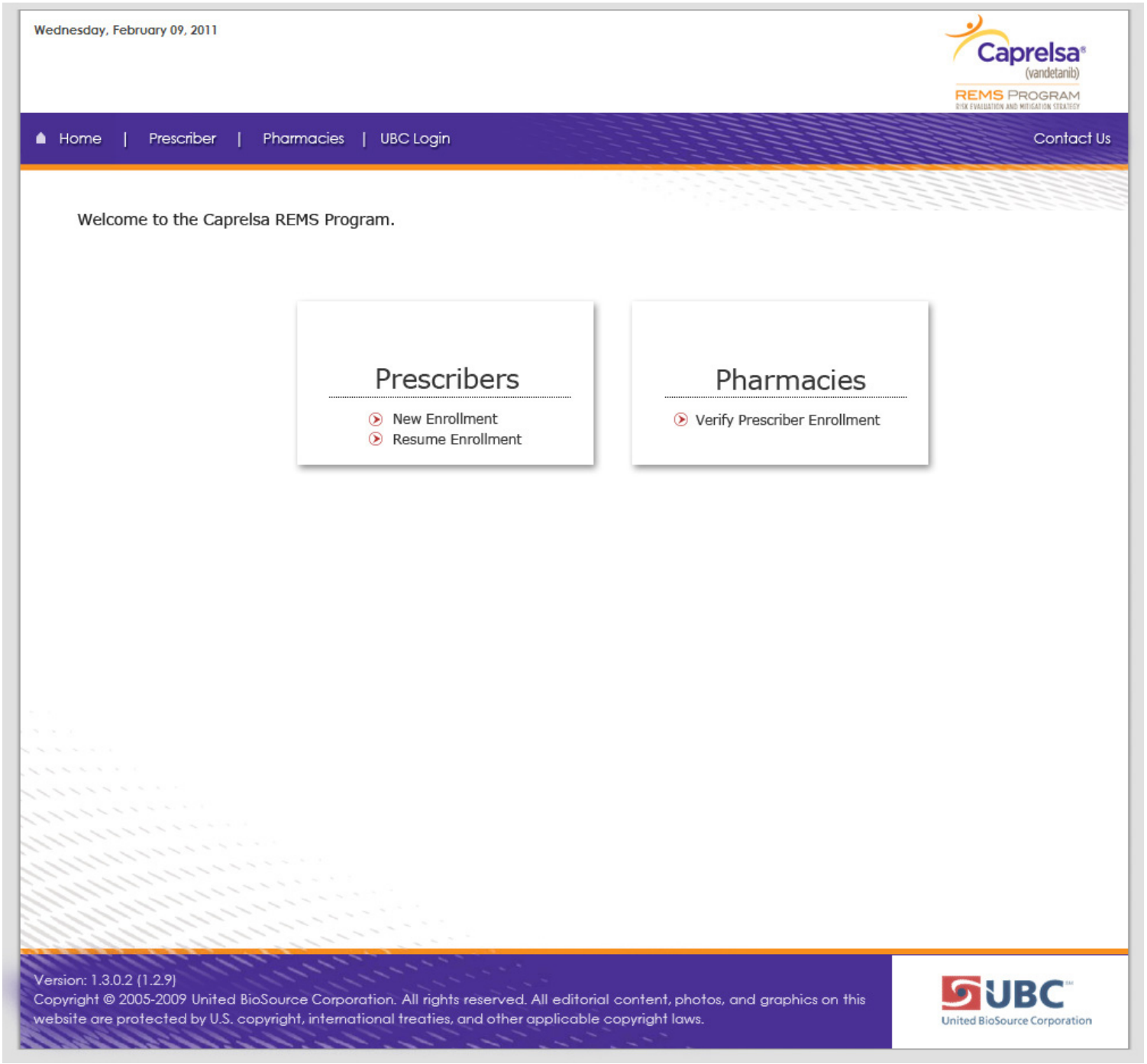
- **CAPRELSA can prolong the QT interval. Torsades de pointes and sudden death have been reported in patients receiving CAPRELSA.**
- **CAPRELSA should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to CAPRELSA administration and should be periodically monitored.**
- **Drugs known to prolong the QT interval should be avoided. If a drug known to prolong the QT interval must be administered, more frequent ECG monitoring is recommended.**

- **Given the half-life of 19 days, ECGs should be obtained to monitor the QT at baseline, at 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA and every 3 months thereafter. Following any dose reduction for QT prolongation, or any dose interruptions greater than 2 weeks, QT assessment should be conducted as described above.**
- **Because of the 19-day half-life, adverse reactions including a prolonged QT interval may not resolve quickly. Monitor appropriately.**
- **Only prescribers and pharmacies certified with the restricted distribution program are able to prescribe and dispense CAPRELSA.**

- Do not use CAPRELSA in patients with congenital long QT syndrome
- Because of the risk of QT prolongation, ECGs and levels of serum potassium, calcium, magnesium, and TSH should be monitored at baseline, at 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA, and every 3 months thereafter and following dose adjustments.
- Severe skin reactions (including Stevens-Johnson syndrome), some leading to death, have been reported and may prompt permanent discontinuation of CAPRELSA.
- Interstitial lung disease (ILD) has been observed with CAPRELSA and deaths have been reported. Interrupt CAPRELSA treatment and investigate unexplained dyspnea, cough, and fever.
- Ischemic cerebrovascular events, serious hemorrhagic events, and heart failure have been observed with CAPRELSA and some cases have been fatal.
- Diarrhea has been observed with CAPRELSA. Serum electrolytes and ECGs should be carefully monitored in cases of diarrhea because of the risk of QT prolongation with CAPRELSA. If severe diarrhea develops, CAPRELSA treatment should be stopped until diarrhea improves.
- Hypothyroidism, hypertension, and reversible posterior leukoencephalopathy syndrome (RPLS) have been observed with CAPRELSA.
- The concomitant use of known strong CYP3A4 inducers may reduce drug levels of CAPRELSA and should be avoided. The administration of CAPRELSA with antiarrhythmic drugs and other drugs that may prolong the QT interval should be avoided.
- CAPRELSA exposure is increased in patients with impaired renal function. The starting dose of CAPRELSA should be reduced to 200 mg in patients with moderate to severe renal impairment and the QT interval should be monitored closely.
- CAPRELSA is not recommended for patients with moderate and severe hepatic impairment, since safety and efficacy have not been established.
- CAPRELSA can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid pregnancy while receiving CAPRELSA and for at least 4 months following treatment.
- The most common adverse drug reactions (>20%) seen with CAPRELSA are diarrhea (57%), rash (53%), acne (35%), nausea (33%), hypertension (33%), headache (26%), fatigue (24%), decreased appetite (21%), and abdominal pain (21%). The most common laboratory abnormalities (>20%) were decreased calcium (57%), increased ALT (51%), and decreased glucose (24%).
- **CAPRELSA REMS Program**: Because of the risks of QT prolongation, Torsades de pointes and sudden death, CAPRELSA is available only through the CAPRELSA REMS program. Only prescribers and pharmacies certified with the restricted distribution program are able to prescribe and dispense CAPRELSA. To learn about the specific REMS requirements and to enroll in the CAPRELSA REMS Program call 1-800-236-9933 or visit www.caprelsarems.com.

Please see the full Prescribing Information for CAPRELSA including boxed WARNING.

Only certified prescribers can prescribe CAPRELSA.
Enroll into the CAPRELSA REMS Program to become certified to prescribe.


Wednesday, February 09, 2011
Caprelsa (vandetanib)
REMS PROGRAM
Home | Prescriber | Pharmacies | UBC Login
Contact Us
Welcome to the Caprelsa REMS Program.
Prescribers
New Enrollment
Resume Enrollment
Pharmacies
Verify Prescriber Enrollment
Version: 1.3.0.2 (1.2.9)
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Page-1.png

Prescriber Training Program

The goal of the Prescriber Training Program is to help ensure that healthcare providers treating patients with Caprelsa® (vandetanib); 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 full 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 been reported in patients administered CAPRELSA (vandetanib)
    - In the phase 3 medullary thyroid cancer clinical trial, there was one sudden death and one death from cardiopulmonary arrest in patients receiving CAPRELSA after data cut-off.
- 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	33 (14%)	18 (8%)	1 (1%)	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
- CAPRELSA has a half-life of 19 days, 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 been reported with CAPRELSA (vandetanib). 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

Patient Selection

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

Use of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because 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
- CAPRELSA treatment should not be started in patients whose QTcF interval is greater than 450 ms
- CAPRELSA should not be given to patients who have a history of
    - Torsades de pointes
    - bradyarrhythmias or
    - uncompensated heart failure
- CAPRELSA has not been studied in patients with ventricular arrhythmias or recent myocardial infarction
- CAPRELSA 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), which of the following statement is true?

a. CAPRELSA is contraindicated in patients with congenital long QT syndrome
b. CAPRELSA should not be given 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

ECG Monitoring

- ECGs should be obtained:
    - At baseline
    - 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA (vandetanib) and every 3 months thereafter
    - Following any dose reduction for QT prolongation or any dose interruptions >2 weeks (monitor as described above)
- Patients who develop QTcF >500 ms should stop taking CAPRELSA until QTcF is <450 ms. CAPRELSA can be resumed at a reduced dose
- ECGs may require more frequent monitoring in cases of diarrhea

Q3. According to the Prescribing Information, patients who develop a QTcF greater than 500 ms while on CAPRELSA (vandetanib) 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

Electrolyte Monitoring

- To help reduce the risk of QT prolongation :
    - Serum potassium levels should be maintained at ≥4 mEq/L (within normal range)
    - Serum magnesium and calcium levels should be kept within normal range
- Levels of serum potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH) should be obtained:
    - At baseline
    - 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA (vandetanib) and every 3 months thereafter
- Electrolytes may require more frequent monitoring in cases of 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	132 (57%)	26 (11%)	27 (27%)	2 (2%)

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

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

Drug Interactions

- Drugs that prolong the QT interval or are associated with Torsades de pointes should be avoided in combination with CAPRELSA (vandetanib)
    - 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 Arizona CERT Web site at www.azcert.org[1]
- If no alternative therapy exists and concomitant treatment with a drug that is known to prolong the QT interval is medically necessary, ECG monitoring of the QT interval should be performed more frequently

References: 1. Arizona Center for Education and Research on Therapeutics (CERT). QT drug lists by risk groups. http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm. Accessed March 21, 2011.

Q5. According to the Prescribing Information, administration of CAPRELSA (vandetanib) 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

Dosing and Administration

- The recommended daily dose is 300 mg of CAPRELSA (vandetanib) taken orally, continued until patients are no longer benefiting from treatment or an unacceptable toxicity occurs
- The 300 mg daily dose may be reduced to 200 mg (two 100 mg tablets) and then to 100 mg based on CTCAE (Common Terminology Criteria for Adverse Events) grade 3 or greater toxicities
- The starting dose should be reduced to 200 mg in patients with moderate (creatinine clearance ≥30 to <50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment. QT interval should be monitored closely
- CAPRELSA may be taken with or without food
- If a patient misses a dose of CAPRELSA, the missed dose should not be taken if it is less than 12 hours before the next dose
- CAPRELSA is available as 100 mg tablets and 300 mg tablets

Q6. According to the Prescribing Information, if a patient misses a dose of CAPRELSA (vandetanib):

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

CAPRELSA is a registered trademark of the AstraZeneca group of companies.

The CAPRELSA REMS Program Pharmacy Enrollment Form

A designated representative from the pharmacy must enroll and be certified by the CAPRELSA REMS Program before the pharmacy can dispense Caprelsa® (vandetanib). Please complete the information below and then continue with certification by clicking the NEXT button on your screen.

Pharmacy Information

Pharmacy Name: _____

Address: _____

City: _____ State: _____ Zip: _____

Phone: _____ Fax: _____

National Provider Identifier (NPI): _____ State License Number: _____

NCPDP Number: _____

1. I understand that CAPRELSA is only available through the CAPRELSA REMS Program and I and pharmacy staff must comply with the program requirements. In addition, as the designated authorized pharmacist, I acknowledge that:
    a. I understand that only prescribers enrolled in the CAPRELSA REMS Program can prescribe CAPRELSA.
    b. The pharmacy must have a system in place to verify that the prescriber is enrolled in the CAPRELSA REMS Program each time CAPRELSA is dispensed. If the prescriber is not enrolled, CAPRELSA cannot be dispensed.
    c. All pharmacy staff and critical employees involved in the dispensing of CAPRELSA will be educated on the risks and requirements of the CAPRELSA REMS Program.
    d. The pharmacy will provide Medication Guide each time CAPRELSA is dispensed.
    e. The pharmacy will ensure that it has adequate processes and procedures in place and that those processes and procedures are being followed for the CAPRELSA REMS Program.
    f. The pharmacy will maintain a system, records and documentation that can be audited to document compliance with the CAPRELSA REMS Program; including prescriber certification each time CAPRELSA is dispensed.

Authorized Pharmacist Signature: _____ Date_____

Title: _____ First Name: _____ Last Name: _____

Phone Number: _____ E-mail: _____

If you have any enrollment questions, please call (1-800-817-2722)
Please visit www.caprelsarems.com **for more information**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L JUSTICE
06/22/2011