

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022405Orig1s000

REMS

Initial REMS Approval: 04/2011

NDA 22-405
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 vandetanib 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 vandetanib.
2. to inform patients about the serious risks associated with vandetanib.

II. REMS ELEMENTS

A. Medication Guide

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

The Medication Guide is part of the Vandetanib 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 vandetanib 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 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 Vandetanib REMS Program Web Site (www.vandetanibrems.com) for 1 year from the date of distribution.

The *Dear Healthcare Provider Letter* is part of the Vandetanib 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 Vandetanib REMS Program website (www.vandetanibrems.com) for 1 year from the date of distribution.

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

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

C. Elements to Assure Safe Use

1. Healthcare providers who prescribe vandetanib are specially certified.

- a. AstraZeneca will ensure that healthcare providers who prescribe vandetanib are specially certified.
- b. To become certified to prescribe vandetanib, prescribers will be required to enroll in the Vandetanib REMS Program and must:
 - 1) Review the vandetanib *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 *Prescriber Enrollment Form* and submit it to the Vandetanib 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 vandetanib REMS. Substantive changes are defined as 1) significant changes to the operation of the Vandetanib REMS Program; 2) changes to the Prescribing Information and Medication Guide that affect the risk benefit profile of vandetanib.

d. AstraZeneca will:

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

The *vandetanib REMS website* (www.vandetanibrems.com) is part of the Vandetanib 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 Vandetanib 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 vandetanib.

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

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

- a. AstraZeneca will ensure that vandetanib will only be dispensed by certified pharmacies. To become certified to dispense vandetanib, each pharmacy must be enrolled in the Vandetanib 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 Vandetanib REMS Program can prescribe vandetanib.
- 2) The pharmacy must have a system in place to verify that the prescriber is enrolled in the Vandetanib REMS Program each time vandetanib is dispensed. If the prescriber is not enrolled, vandetanib cannot be dispensed.
- 3) All pharmacy staff and critical employees involved in the dispensing of vandetanib will be educated on the risks and requirements of the Vandetanib REMS Program.
- 4) The pharmacy will provide the Medication Guide each time vandetanib 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 Vandetanib REMS Program.
- 6) The pharmacy will maintain a system, records and documentation that can be audited to document compliance with the Vandetanib REMS Program; including prescriber certification each time vandetanib is dispensed.
- 7) Complete and sign the *Pharmacy Enrollment Form* and submit it to the Vandetanib REMS Program.

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

D Implementation System

1. AstraZeneca will ensure that pharmacies (including pharmacy distributors) dispensing vandetanib are specially certified using the criteria described above.
2. AstraZeneca will ensure that distributors who distribute vandetanib are specially certified. Specially certified distributors will agree to:
 - a. Distribute vandetanib only to pharmacies certified in the vandetanib REMS.
 - b. Put processes and procedures in place to ensure that the requirements of the vandetanib REMS are followed.
 - c. Agree to be audited to ensure that vandetanib 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 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 vandetanib 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 Vandetanib 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 Vandetanib REMS Program will be available through the REMS website (www.vandetanibrems.com) or by calling the Call Center at 1-800-236-9933.
7. If there are substantive changes to the Vandetanib 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 Vandetanib REMS Program
 - b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of vandetanib.
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 Vandetanib 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 Vandetanib REMS Program to the FDA every 6 months for the first year following the approval of the vandetanib 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.

IMPORTANT DRUG WARNING

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

DATE

Dear Healthcare Provider:

AstraZeneca Pharmaceuticals LP would like to inform you of the approval of 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 vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib.

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

In order to prescribe vandetanib, you must:

- Read this Healthcare Provider (HCP) Letter; review HCP Education Pamphlet or HCP REMS Education Slide Set; and the vandetanib full Prescribing Information
- Complete the Prescriber Training Program (online or phone)
- Complete prescriber enrollment form

To ENROLL, visit www.vandetanibrems.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 vandetanib.

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

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

IMPORTANT DRUG WARNING

SUBJECT: Serious Risks of QT prolongation, Torsades de pointes and Sudden death for 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 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 vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib.

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

In order to prescribe vandetanib, prescribers must:

- Read the Healthcare Provider (HCP) Letter; review HCP Education Pamphlet or HCP REMS Education Slide Set; and the vandetanib full Prescribing Information
- Complete the Prescriber Training Program (online or phone)
- Complete prescriber enrollment form

To ENROLL, visit www.vandetanibrems.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 vandetanib REMS website at www.vandetanibrems.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 vandetanib.

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

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

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Important Information for Healthcare Providers About the Risk of QT Prolongation, Torsades de Pointes, and Sudden Death With Vandetanib

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

In order to prescribe vandetanib, a physician must:

- Review the educational materials, including:
 - Risk information regarding QT prolongation, Torsades de pointes, and sudden death with vandetanib
 - Considerations for patient selection
 - ECG and electrolyte monitoring requirements
 - Drug interaction information
 - Dosage and administration information
- Complete the prescriber training program
- Complete prescriber enrollment form

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

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

A prescriber must enroll in the Vandetanib REMS Program to prescribe 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 vandetanib is only available through the Vandetanib 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 vandetanib, and I have completed the prescriber training program.
2. I understand that vandetanib is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib.
3. **Risk of QT prolongation, Torsades de pointes, and Sudden Death**
 - a. I understand that vandetanib can prolong the QT interval in a concentration-dependent manner, and that Torsades de pointes and sudden death have been reported in patients administered vandetanib.
 - b. I understand that a prolonged QT interval may NOT resolve quickly because of the 19-day half-life.
 - c. I understand that vandetanib 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.

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

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 vandetanib **and every 3 months** thereafter.
- b. Patients who develop a QTcF greater than 500 ms should stop taking vandetanib until QTcF returns to less than 450 ms. Dosing of vandetanib 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. Vandetanib should not be used in patients with hypocalcemia, hypokalemia, and/or hypomagnesemia.
- b. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to vandetanib 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 vandetanib.

7. Dosing – I understand

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

Prescriber Signature: _____ Date: _____



REMS PROGRAM
RISK EVALUATION AND MITIGATION STRATEGY

**Vandetanib and Risk of QT Prolongation,
Torsades de Pointes and Sudden Death**

Healthcare Provider Education Pamphlet

Important Risk Evaluation and Mitigation
Strategy (REMS) Information for
Healthcare Providers



Introduction

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

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

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

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

About This Pamphlet

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

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 vandetanib. These are not the only risks associated with vandetanib. Please see the accompanying full Prescribing Information for vandetanib, including the boxed WARNING.

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

Prescriber and Pharmacy Certification in the Vandetanib REMS Program

Only prescribers enrolled in the Vandetanib REMS Program can prescribe vandetanib

In order to prescribe vandetanib, you must:

Read the Dear Healthcare Provider (HCP) Letter; review this Healthcare Provider Education pamphlet or HCP REMS Education Slide Set; and the vandetanib Full Prescribing Information

Step 1



Complete the Prescriber Training Program (online or phone)

Step 2



Complete prescriber enrollment form

Step 3

To ENROLL, visit www.vandetanibrems.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 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 Vandetanib REMS Program can dispense vandetanib

- Vandetanib 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 Vandetanib 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 vandetanib 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

QT Prolongation, Torsades de Pointes, and Sudden Death

- Torsades de pointes, ventricular tachycardia, and sudden deaths have been reported in patients administered vandetanib
 - In the phase 3 medullary thyroid cancer clinical trial, there was one sudden death and one death from cardiopulmonary arrest in patients receiving vandetanib after data cut-off
- Vandetanib can prolong the QT interval in a concentration-dependent manner
 - In 231 medullary thyroid cancer patients randomized to receive vandetanib 300 mg once daily in the phase 3 clinical trial, vandetanib was associated with sustained plasma concentration-dependent QT prolongation

	Vandetanib 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 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 vandetanib, 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 vandetanib experienced >60 ms increase in Δ QTcF
- Because vandetanib 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.



Patient Selection

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

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

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

Considerations for Patient Selection

- Do not use vandetanib in patients with congenital long QT syndrome
- Vandetanib treatment should not be started in patients whose QTcF interval is greater than 450 ms
- Vandetanib should not be given to patients who have a history of:
 - Torsades de pointes
 - Bradyarrhythmias or
 - Uncompensated heart failure
- Vandetanib 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 vandetanib. These are not the only risks associated with vandetanib. Please see the accompanying full Prescribing Information for vandetanib, including the Boxed WARNING.

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

ECG Monitoring

- ECGs should be obtained:
 - At baseline
 - 2 to 4 weeks and 8 to 12 weeks after starting treatment with 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 vandetanib until QTcF is <450 ms. Vandetanib 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 to 4 weeks and 8 to 12 weeks after starting treatment with 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 vandetanib compared with placebo

	Vandetanib 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%)



Recommendations for ECG Monitoring

- ECGs should be obtained:
 - At baseline
 - 2 to 4 weeks and 8 to 12 weeks after starting treatment with 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 vandetanib until QTcF is <450 ms. Vandetanib 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 to 4 weeks and 8 to 12 weeks after starting treatment with vandetanib and every 3 months thereafter
- Electrolytes may require more frequent monitoring in cases of diarrhea

Drug Interactions

- Drugs that prolong the QT interval or are associated with Torsades de pointes should be avoided in combination with 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, pimozone)
 - For lists of other possible or conditional risk drugs, please visit the Arizona CERT Web site at www.azcert.org¹
- 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 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
- Vandetanib may be taken with or without food
- If a patient misses a dose of vandetanib, the missed dose should not be taken if it is less than 12 hours before the next dose
- Vandetanib is available as 100-mg tablets and 300-mg tablets

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



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

- Vandetanib can prolong the QT interval. Torsades de pointes and sudden death have been reported in patients receiving vandetanib.
- Vandetanib should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to vandetanib 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 vandetanib 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 vandetanib.

Please see accompanying full Prescribing Information for vandetanib.



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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

ATLAS #1153205 04/11



Introduction

- This presentation has been developed as part of the Vandetanib REMS Program, a restricted distribution program, to help educate physicians on the serious risks of QT prolongation, Torsades de pointes, and sudden death associated with vandetanib
- Vandetanib is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib
- 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, and
 - Appropriate dosing and administration
- This presentation focuses on the risks of QT prolongation, Torsades de pointes, and sudden death associated with vandetanib. These are not the only risks associated with vandetanib. Please see the full Prescribing Information for vandetanib, including the Boxed Warning



Prescriber and Pharmacy Certification in the Vandetanib REMS Program

- **Only prescribers enrolled in the Vandetanib REMS Program can prescribe vandetanib**
 - In order to prescribe vandetanib, you must:
 - Read the Dear Healthcare Provider (HCP) Letter; review this HCP REMS Education Slide Set or HCP Education pamphlet; and the vandetanib full Prescribing Information
 - Complete the Prescriber Training Program (online or phone)
 - Complete prescriber enrollment form
 - To ENROLL, visit www.vandetanibrems.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 vandetanib 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 Vandetanib REMS Program can dispense vandetanib**
 - Vandetanib is available through Biologics Inc. Call 1-800-236-9933 or go to www.biologics.today.com for more information



QT Prolongation, Torsades de pointes, and Sudden Death

- Torsades de pointes, ventricular tachycardia, and sudden deaths have been reported in patients administered vandetanib
 - In the phase 3 medullary thyroid cancer clinical trial, there was one sudden death and one death from cardiopulmonary arrest in patients receiving vandetanib after data cut-off
- Vandetanib can prolong the QT interval in a concentration-dependent manner
 - In 231 medullary thyroid cancer patients randomized to receive vandetanib 300 mg once daily in the phase 3 clinical trial, vandetanib was associated with sustained plasma concentration-dependent QT prolongation

	Vandetanib 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%)



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

- In the phase 3 medullary thyroid cancer clinical trial:
 - Among all patients who received vandetanib, 69% had QT prolongation >450ms and 7% had QT prolongation >500ms by ECG using Fridericia correction (QTcF)
 - Based on the exposure-response relationship, among all patients who received vandetanib, 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 vandetanib experienced greater than 60 ms increase in Δ QTcF
- Vandetanib has a half-life of 19 days, adverse reactions including prolonged QT interval may not resolve quickly. Monitor appropriately



Patient Selection

- In addition to thinking about the risks of QT prolongation, Torsades de pointes and sudden death associated with vandetanib, consider the following when deciding if a patient is appropriate for vandetanib treatment:
 - Do not use vandetanib in patients with congenital long QT syndrome
 - Vandetanib treatment should not be started in patients whose QTcF interval is greater than 450 ms
 - Vandetanib should not be given to patients who have a history of
 - Torsades de pointes
 - bradyarrhythmias or
 - uncompensated heart failure
 - Vandetanib 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 vandetanib. These are not the only risks associated with vandetanib. Please see the full Prescribing Information for vandetanib, including the Boxed Warning



ECG Monitoring

- ECGs should be obtained:
 - At baseline
 - 2-4 weeks and 8-12 weeks after starting treatment with 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 vandetanib until QTcF is <450 ms. Vandetanib 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 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 vandetanib compared to placebo

	Vandetanib 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%)



Drug Interactions

- Drugs that prolong the QT interval or are associated with Torsades de pointes should be avoided in combination with vandetanib
 - These include:
 - **Antiarrhythmic drugs:** Including but not limited to amiodarone, disopyramide, procainamide, sotalol, dofetilide
 - **Other drugs:** Including but not limited to cloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, pimozide
 - For lists of other possible or conditional risk drugs, please visit the Arizona CERT Website at www.azcert.org¹
- 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.



Dosing and Administration

- The recommended daily dose is 300 mg of 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
- Vandetanib may be taken with or without food
- If a patient misses a dose of vandetanib, the missed dose should not be taken if it is less than 12 hours before the next dose
- Vandetanib is available as 100-mg tablets and 300-mg tablets



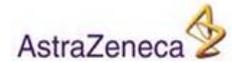
WARNING: QT Prolongation, Torsades de Points, and Sudden Death

- **WARNING: QT PROLONGATION, TORSADES DE POINTES, AND SUDDEN DEATH**
- Vandetanib can prolong the QT interval. Torsades de pointes and sudden death have been reported in patients receiving vandetanib.
- Vandetanib should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to vandetanib 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 vandetanib 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 vandetanib.





For US audiences only



Prescribing vandetanib

[Important Safety Information Including Boxed WARNING](#)

[Approved Indication](#)

[Full Prescribing Information for vandetanib](#) 

[Medication Guide for vandetanib](#) 

[Vandetanib Prescription Form](#) 

Welcome to the Vandetanib REMS Program

Vandetanib, a kinase inhibitor, 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 vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib.

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

The Vandetanib 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 vandetanib

Under the Vandetanib REMS Program, only certified prescribers can prescribe vandetanib.

Vandetanib REMS Program: Learn and Enroll

[Learn About the Vandetanib REMS Program](#)

[Enroll Into the Vandetanib REMS Program](#)

REMS Home

[Educational Materials](#)

[Learn About the Vandetanib REMS Program](#)

[Enroll Into the Vandetanib REMS Program](#)

[Contact Us](#)

Indication

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

Important Safety Information, including boxed WARNING

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

- Vandetanib can prolong the QT interval. Torsades de pointes and sudden death have been reported in patients receiving vandetanib.
- Vandetanib should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to vandetanib 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 vandetanib 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 vandetanib.**
-
- Do not use vandetanib 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 vandetanib, 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 vandetanib.
 - Interstitial lung disease (ILD) has been observed with vandetanib and deaths have been reported. Interrupt vandetanib treatment and investigate unexplained dyspnea, cough, and fever.
 - Ischemic cerebrovascular events, serious hemorrhagic events, and heart failure have been observed with vandetanib and some cases have been fatal.
 - Diarrhea has been observed with vandetanib. Serum electrolytes and ECGs should be carefully monitored in cases of diarrhea because of the risk of QT prolongation with vandetanib. If severe diarrhea develops, vandetanib treatment should be stopped until diarrhea improves.
 - Hypothyroidism, hypertension, and reversible posterior leukoencephalopathy syndrome (RPLS) have been observed with vandetanib.
 - The concomitant use of known strong CYP3A4 inducers may reduce drug levels of vandetanib and should be avoided. The administration of vandetanib with antiarrhythmic drugs and other drugs that may prolong the QT interval should be avoided.
 - Vandetanib exposure is increased in patients with impaired renal function. The starting dose of vandetanib should be reduced to 200 mg in patients with moderate to severe renal impairment and the QT interval should be monitored closely.
 - Vandetanib is not recommended for patients with moderate and severe hepatic impairment, since safety and efficacy have not been established.
 - Vandetanib can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid pregnancy while receiving vandetanib and for at least 4 months following treatment.
 - The most common adverse drug reactions (>20%) seen with vandetanib 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%).
 - **Vandetanib REMS Program:** Because of the risks of QT prolongation, Torsades de pointes and sudden death, vandetanib is available only through the vandetanib REMS program. Only prescribers and pharmacies certified with the restricted distribution program are able to prescribe and dispense vandetanib. To learn about the specific REMS requirements and to enroll in the Vandetanib REMS Program call 1-800-817-2722 or visit www.vandetanibrems.com.

Please see the full [Prescribing Information for vandetanib](#) including boxed WARNING. 

Only certified prescribers can prescribe vandetanib.
[Enroll](#) into the Vandetanib REMS Program to become certified to prescribe.



Vandetanib

Welcome to the Vandetanib REMS Program.

Prescribers

- ▶ New Enrollment
- ▶ Resume Enrollment

Pharmacies

- ▶ Verify Prescriber Enrollment

Prescriber Training Program Questions

The goal of the Prescriber Training Program is to help ensure that Healthcare Providers treating patients with vandetanib understand the risk for QT prolongation, Torsades de pointes and sudden death associated with vandetanib treatment. These are not the only risks associated with vandetanib. Please see the full Prescribing Information for additional Warnings and Precautions and safety information on vandetanib.

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 vandetanib
 - In the phase 3 medullary thyroid cancer clinical trial, there was one sudden death and one death from cardiopulmonary arrest in patients receiving vandetanib after data cut-off.
- Vandetanib can prolong the QT interval in a concentration-dependent manner
 - In 231 medullary thyroid cancer patients randomized to receive vandetanib 300 mg once daily in the phase 3 clinical trial, vandetanib was associated with sustained plasma concentration-dependent QT prolongation.

	Vandetanib 300mg 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 vandetanib, 69% had QT prolongation >450ms and 7% had QT prolongation >500ms by ECG using Fridericia correction (QTcF)
- Based on the exposure-response relationship, among all patients who received vandetanib, 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 vandetanib experienced greater than 60 ms increase in Δ QTcF
- Vandetanib 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 vandetanib. Vandetanib 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

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

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

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

- Do not use vandetanib in patients with congenital long QT syndrome
- Vandetanib treatment should not be started in patients whose QTcF interval is greater than 450 ms
- Vandetanib should not be given to patients who have a history of
 - Torsades de pointes
 - bradyarrhythmias or
 - uncompensated heart failure
- Vandetanib 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 vandetanib is the appropriate treatment. This material focuses on the risks of QT prolongation, Torsades de pointes, and sudden death associated with vandetanib. These are not the only risks associated with vandetanib. Please see the full Prescribing Information for vandetanib, including the Boxed Warning.

Q2. According to the Prescribing Information, Which of the following statement is true?

- a. Vandetanib is contraindicated in patients with congenital long QT syndrome
- b. Vandetanib should not be given to patients with a history of Torsades de pointes, bradyarrhythmias, or uncompensated heart failure
- c. Vandetanib 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 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 vandetanib until QTcF is <450 ms. Vandetanib 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 vandetanib treatment should:

- a. Continue vandetanib without interruption, at the current dose
- b. Continue vandetanib without interruption, but at a reduced dose
- c. Stop taking vandetanib until QTcF returns to less than 450ms. Dosing of vandetanib 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 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 vandetanib compared to placebo

	Vandetanib 300mg 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 vandetanib:

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

Drug Interactions

- Drugs that prolong the QT interval or are associated with Torsades de pointes should be avoided in combination with vandetanib
 - These include antiarrhythmic drugs (including but not limited to amiodarone, disopyramide, procainamide, sotalol, dofetilide) and other drugs (including but not limited to cloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, pimozide)
 - For lists of other possible or conditional risk drugs, please visit the Arizona CERT Website at www.azcert.org¹
- 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 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 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
 - Vandetanib may be taken with or without food
 - If a patient misses a dose of vandetanib, the missed dose should not be taken if it is less than 12 hours before the next dose
 - Vandetanib is available as 100-mg tablets and 300-mg tablets
-

Q6. According to the Prescribing Information, if a patient misses a dose of 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
-

The Vandetanib REMS Program Pharmacy Enrollment Form

A designated representative from the pharmacy must enroll and be certified by the Vandetanib REMS Program before the pharmacy can dispense 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 vandetanib is only available through the Vandetanib 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 Vandetanib REMS Program can prescribe vandetanib.
 - b. The pharmacy must have a system in place to verify that the prescriber is enrolled in the Vandetanib REMS Program each time vandetanib is dispensed. If the prescriber is not enrolled, vandetanib cannot be dispensed.
 - c. All pharmacy staff and critical employees involved in the dispensing of vandetanib will be educated on the risks and requirements of the Vandetanib REMS program.
 - d. The pharmacy will provide Medication Guide each time vandetanib 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 Vandetanib REMS Program.
 - f. The pharmacy will maintain a system, records and documentation that can be audited to document compliance with the Vandetanib REMS Program; including prescriber certification each time vandetanib 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.vandetanibrems.com for more information

1

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

/s/

RICHARD PAZDUR
04/06/2011