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 healthcare providers 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 HCP Education pamphlet or HCP REMS Education Slide Set; and the vandetanib 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.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.biologicstoday.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

Please see boxed WARNING on page 10 and accompanying full Prescribing Information.
**QT Prolongation, Torsades de Pointes, and Sudden Death**

- Torsades de pointes, ventricular tachycardia, and sudden deaths have 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

<table>
<thead>
<tr>
<th>ECG QT prolonged</th>
<th>Vandetanib 300 mg N=231</th>
<th>Placebo N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>33 (14%)</td>
<td>18 (8%)</td>
<td>1 (1%)</td>
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</tbody>
</table>

- 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 ($\Delta$QTcF) was 35 (33-36) ms for the 300 mg dose. The $\Delta$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 $\Delta$QTcF
- Because vandetanib has a half-life of 19 days, adverse reactions including prolonged QT interval may not resolve quickly. Monitor appropriately
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 >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
Recommendations for Electrolyte Monitoring

- To help reduce the risk of QT prolongation:
  - Serum potassium levels should be maintained at $\geq 4$ 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

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

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 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
- 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


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 (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
- 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 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.