CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

FINAL REMS REVIEW

Date:	April 6, 2011
To:	Robert Justice, M.D., Director Division Drug Oncology Products (DDOP)
Through:	Claudia Karwoski, Pharm.D. Director Division of Risk Management (DRISK)
From:	**Scientific Lead,** Risk Management Analyst (RMA) Suzanne Robottom, Pharm.D., DRISK Kate Heinrich, MA., Health Education Reviewer, DRISK
Subject:	Review of Risk Evaluation and Mitigation Strategy
Drug Name:	vandetanib
Application Type/Number:	NDA 22405
Applicant:	AstraZeneca
OSE RCM #:	2010-1503

Reference ID: 2928794

1 INTRODUCTION

The FDA is reviewing an application for vandetanib, a kinase inhibitor, for the treatment of unresectable, locally advanced or metastatic medullary thyroid carcinoma (MTC). AstraZeneca did not propose a Risk Evaluation and Mitigation Strategy (REMS) for this product in the original application.

In the vandetanib safety database (N=3019), the mean increase in QTc interval was approximately 35ms for vandetanib treated patients. More than 35% of patients experienced > 60ms increase in QTc. There were 11 cases of sudden death and 2 documented cases of Torsades de pointes (TdP). Two of the 11 cases occurred in the Phase 3 clinical trial in MTC. The other 9 cases occurred trials for treatment with vandetanib for other malignancies.

After discussion and agreement at a Safety First Steering Committee meeting on December 21, 2010, a REMS Notification Letter was issued on January 13, 2011 requiring a REMS consisting of a Medication Guide, Communication Plan, and elements to assure safe use (ETASU; prescriber certification, pharmacy certification), implementation system, and timetable for submission of assessments. QT prolongation, Torsades de pointes, and sudden death are included in a Boxed Warning in the label.

This application received a priority review. It originally had a PDUFA goal date of January 7, 2011. This date was extended to April 7, 2011 because the applicant submitted a major amendment to the application.

2 MATERIALS REVIEWED

We reviewed the following submissions:

- Proposed REMS and REMS Supporting Document, submissions of February 17, 2011, March 22, 2011, March 23, 2011, April 6, 2011

3 RESULTS OF REVIEW OF PROPOSED YERVOY RISK EVALUATION AND MITIGATION STRATEGY

3.1 Goal

The goals of the REMS are to:

- 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.
- to inform patients about the serious risks associated with vandetanib.

3.2 REMS Elements

3.2.1 Communication Plan

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The REMS for vandetanib includes a communication plan to healthcare providers (HCPs) expected to prescribe vandetanib. This includes oncologists, endocrinologists, and surgeons. A DHCP Letter will be sent to those medical specialties. A Dear Professional Society Letter will be disseminated to the following professional societies:

- American Society of Clinical Oncology (ASCO)
- American Thyroid Association (ATA)
- National Comprehensive Cancer Network (NCCN)
- Oncology Nursing Society (ONS)

Other educational materials (outlined below) will be disseminated in conjunction with these DHCP letters. These two letters will be available on the vandetanib REMS website for 1 year.

In addition, AstraZeneca proposed and we agreed that AstraZeneca will display a convention panel outlining the details of the REMS Program at conferences associated with ASCO, ATA, NCCN, and ONS if vandetanib product information is displayed.

3.2.2 Elements to Assure Safe Use

A. Healthcare providers who prescribe vandetanib are specially certified.

All healthcare providers who prescribe vandetanib will be certified. To become certified, a prescriber must complete the following requirements to be enrolled:

1) Review the vandetanib *REMS HCP Education Pamphlet* or *Slide Set* and the Full Prescribing Information, including the Medication Guide.

2) Complete the *Prescriber Training* either online or via the telephone.

   Reviewer Comment: The Prescriber Training consists of the same content as included in the Education Pamphlet and slide set. (b) (4) [redacted]

3) Complete and sign the *Prescriber Enrollment Form* (online or via the telephone) and submit it to the vandetanib REMS Program.

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

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

Review Comment: We verbally clarified with AstraZeneca that FDA would discuss with AstraZeneca a substantive change.

To implement this element, AstraZeneca will:

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

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 slide 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.

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

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

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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 a 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.

   Reviewer Comment: AstraZeneca has contracted with a specialty pharmacy to dispense vandetanib. At present, AstraZeneca does not plan to distribute vandetanib in retail pharmacies.

3.2.3 Implementation System

The implementation system includes the following:

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 allow that the requirements of the vandetanib REMS are followed.

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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). The database allows certified prescribers to enroll themselves. Certified pharmacies can access the database to verify prescriber enrollment status as required by the REMS. (b) (4)

4. AstraZeneca will monitor distribution data 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 instituted by AstraZeneca for the prescribers, pharmacies, or distributors if noncompliance is found.
   a. Inpatients in acute care settings will be shipped drug per patient if the prescriber is enrolled in the REMS

   b. Long-term care patients will be shipped drug per patient if the prescriber is enrolled in the REMS

   c. All shipments of vandetanib will be accompanied by the Medication Guide.

5. AstraZeneca will monitor and audit the 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.

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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.

3.2.4 Timetable for Submission of Assessments

AstraZeneca will submit REMS Assessments to FDA every six months for the first year and annually thereafter from the date of approval of the REMS.

3.3 REMS Assessment Plan

The REMS assessment reports will include the following:

a. With regard to the assessment of the Medication Guide:
   i. An evaluation of patients' understanding of the serious risks of vandetanib.
   ii. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
   iii. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

b. With regard to the assessment of the communication plan:
   i. The date of product launch and the launch of the communication plan
   ii. The date(s) of mailing and number of recipients of the Dear Healthcare Provider (DHCP) letter and Dear Professional Society Letter
   iii. The number of mailings returned
   iv. The sources of the recipient lists
   v. A copy of all documents included in each mailing
   vi. The dates of any conferences attended

c. With regard to Prescriber Certification:

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i. The number of healthcare providers accessing the training program (during the reporting period and cumulative).
ii. The number of healthcare providers who complete the training program but do not complete enrollment (during the reporting period and cumulative).
iii. The number of healthcare providers enrolled in the vandetanib REMS (during the reporting period and cumulative) and stratify by prescriber specialty.
iv. A summary of the method prescribers used to enroll (online or phone).
v. Proportion of prescribers that correctly answer each training program question and stratify by specialty.
vi. The number of enrolled healthcare providers actively prescribing vandetanib during the reporting period (i.e., have written at least one prescription in the in the time period).
vii. The number of healthcare providers who have ordered/prescribed vandetanib who were not enrolled (during the reporting period and cumulative).

d. With regard to Pharmacy Certification and distributors:
   i. The number of pharmacies enrolled (during the reporting period and cumulative).
   ii. The number of pharmacies ordered/dispensed vandetanib who were not enrolled.
   iii. The number of distributors that distributed vandetanib who were not enrolled (during the reporting period and cumulative).

e. With regard to risk of QT prolongation, Torsades de pointes, and sudden death:
   i. An *analysis* of the post-marketing cases for Torsades de pointes or sudden death reported in association with vandetanib to AstraZeneca (during the reporting period and cumulative) with attention to possible factors that prolonged the QTc (interacting medication initiated, change in patient's health status, failure to adjust dose, lack of ECG monitoring, lack of electrolyte monitoring, etc.).
   ii. The number of patients who were dispensed vandetanib (during the reporting period and cumulative).
   iii. An evaluation of healthcare providers' understanding of the serious risk of vandetanib.

f. Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

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g. Specification of measures that would be taken to increase awareness if surveys of patients or healthcare providers indicate that awareness is not adequate.

h. Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

The sponsor has been asked and they agree to submit the survey methodology and survey instruments for FDA review at least 90 days before the evaluation using the survey is conducted.

4 DISCUSSION/CONCLUSION

The use of an ETASU-based REMS to address the risk of QT prolongation, Torsades de points, and sudden death was discussed at the Safety First Steering Committee meeting December 21, 2010. The committee agreed that an ETASU REMS was appropriate given the severity of the risk (substantial QT prolongation effect and the increased risk of sudden death), long natural history of MTC, and uncertainty around the prescribing population. See the appended SFSC background document for a further information regarding the risk benefit characterization.

There are other notable, serious risks of concern associated with vandetanib that have resulted in hospitalization and death during the development program, including Stevens-Johnson Syndrome and interstitial lung disease. Addressing these risks through a communication plan was discussed. Ultimately, it was determined that these adverse reactions could be managed through routine labeling at this time. These are listed in the Warnings and Precautions section of the label.

At present, AstraZeneca does not have an approved proprietary name for vandetanib. We note that all REMS materials will need to be revised to include the proprietary name and the the sponsor will need to submit a REMS modification.

5 RECOMMENDATION

The REMS submitted April 6, 2011 is acceptable. The REMS should be approved.

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We note that the there minor editorial revisions that Astra Zeneca could not address before submitting. These editorial issues do not affect the risk messaging. These should be addressed when the REMS is modified to include the final approved trade name.

ATTACHMENTS

- December 21, 2010 Vandetanib SFSC Background document
- Interim comments dated February 23, 2011, March 10, 2011, and March 31, 2011
- Final REMS document and all appended materials

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Safety First Steering Committee
December 21, 2010

BACKGROUND DOCUMENT **Drug:** Vandetanib (NDA # 22-405)
Risk: QT prolongation/sudden death

REGULATORY HISTORY

(b) (4)

The sponsor resubmitted vandetanib for the treatment of unresectable, locally advanced or metastatic medullary thyroid carcinoma (MTC) in July 2010, This is a priority review given the orphan disease status.

If approved, vandetanib 300 mg will be the only approved product to treat MTC.

RISK BENEFIT CHARACTERIZATION

There are several risks of concern associated with vandetanib that have resulted in hospitalization and death during the development program, among them are: 1) QT prolongation; 2) Stevens-Johnson Syndrome (SJS); and 3) interstitial lung disease (ILD). In the phase 3 safety database, deaths due to adverse events within 30 days of last treatment occurred in 3% of patients on vandetanib compared to 1% in the placebo. This document focuses on QT prolongation as it is primary driver in considering elements to assure safe use.

There are a number of factors to consider when determining the most appropriate course of action to address a serious risk:

- **Severity of the risk**
  In the vandetanib safety database (N=3019), there were 11 cases of sudden death and 2 documented cases of torsades de pointe (TdP). Two of the 11 cases occurred in the Phase 3 clinical trial in MTC. In this trial, an additional patient died of acute heart failure and arrhythmia. There were no cases of sudden death or arrhythmia in the placebo arm. The mean increase in QTc interval was approximately 35ms for vandetanib treated patients. More than 35% of patients experienced > 60ms increase in QTc. For context, the following products are associated with increased QTc.

Drug	Indication	Mean ΔQTcF, msec	Risk in label	Labeling	REMS
Vandetanib	**MTC**	**35**			
Arsenic Trioxide (IV)	Relapsed APL	47	TdP	BW	No. Given inpt, monitored setting per std practice.
Nilotinib (oral)	CML	18	Sudden Death	BW	Yes. MG+CP
Dofetilide (oral)	Atrial Fibrillation	23	TdP	BW, bolded Warning	Yes, (deemed) MG+ETASU (req hosp admin x 3D)
Sotalol (oral)	Atrial Fibrillation	40	TdP	BW, bolded Warning	No. (label req hosp admin x 3D)
Thioridazine (oral)	Anti-psychotic	30	QT/TdP/sudden death	BW	No.
					(b) (4)
Sunitinib (oral)	Advanced RCC & GIST tumors	14.5	TdP (<0.1%)	W/P	Not for QT (MG on REMS for hepatotoxicity)
					(b) (4)

BW = Boxed Warning, W/P = Warnings and Precautions, CP = Communication Plan

According to ICH E14, "drugs that prolong the mean QT/QTc interval by > 20ms have a substantially increased likelihood of being proarrhythmic."

In considering the risk factors for QT prolongation, MTC patients may be at an increased risk for certain factors as follows:

Risk Factor	MTC patient's possible increased risk
• Hypocalcemia	Increased risk if patients has had parathyroidectomy
• Electrolyte imbalance (Mg, K)	Increased risk because diarrhea is a common side effect of MTC and is further exacerbated in MTC patients treated with vandetanib
• Bradycardia	Increased risk if patient is hypothyroid
• Concomitant use of QT prolonging drugs	Increased risk with possible use of QT prolonging medications like anti-emetics and anti-depressants, which are common co-morbidities in MTC patients
• Heart Failure	No increased risk in MTC patients
• Long QT Syndrome	
• Female Gender	

Therefore, QTc prolongation resulting in sudden death is a significant and serious concern particularly for a disease with a long natural history (10-year survival of approximately 40%).

QT prolongation can be detected via ECG monitoring. While monitoring can be done periodically, the heart's activity fluctuates and periodic monitoring only provides information on the heart's activity at that time point. It is not practical to subject a patient to "round the clock" monitoring. Further, vandetanib has a long half-life (~19 days). Therefore, reducing the dose or discontinuing vandetanib will not produce an instantaneous risk reduction. If a patient begins treatment with medication that inhibits vandetanib's metabolism, this would further slow reduction in plasma concentration and increase risk for an arrhythmia and sudden death.

In summary, beyond informing healthcare providers and patients about the risks, appropriate monitoring, and awareness of signs and symptoms, there is not a complete, foolproof option to prevent these events from happening.

→ *Risk in context of drugs in class, among other drugs used to treat disease*
There are no approved products to treat MTC. Treatment may include adriamycin, cisplatin, dacarbazine (DTIC), sorafenib, or sunitinib. These are used infrequently, have no proven benefit and substantial toxicity.

Briefly, adriamycin (intravenous) is associated with cardiotoxicity, severe myelosuppression, and secondary leukemia. Cisplatin (intravenous) is associated with cumulative renal toxicity, myelosuppression, and neurotoxicity reactions. Dacarbazine (intravenous) is associated with myelosuppression and hepatic necrosis. None of these drugs have REMS and consent prior to treating with these medications is not standard practice.

Sorafenib (oral) is not associated with QT prolongation while sunitinib (oral) is and carries a Warning/Precaution.

→ *Prescribers familiarity with risk, monitoring, and management*
There are a number of oncology products (treatment and supportive care) that prolong QT. In addition, oncologists are used to monitoring for and managing side effects caused by drug treatment. However, it is difficult to anticipate how this drug will be viewed by oncologists who prescribe toxic drug products routinely. It may be that they are less concerned (and thus less vigilant) with this drug and its relative risk compared to other, more toxic drugs. Or, oncologists may be more accepting of necessary monitoring because of an enhanced infrastructure for close follow-up as part of routine oncologic care.

Endocrinologists, not oncologists, typically treat MTC and made up the majority of the primary investigators in the clinical studies. You could argue that endocrinologists are not as used to monitoring drug treatment as closely but you could also argue that they may be more risk adverse (and thus cautious) as a result.

Furthermore, there is a misperception by both patients and prescribers that oral medications are "safer" and require less frequent monitoring. Given that vandetanib has a mean ΔQTc more in keeping with an anti-arrhythmic, it is imperative that clinicians realize the risk their patients will be under while taking this medication, and that absence of symptoms, does not necessarily mean everything is ok.

Due to the many variables listed above, it is difficult to predict who will primarily prescribe vandetanib and how the risk and drug treatment will be perceived. The target prescriber group does affect how a REMS is designed to some extent so this is a complicating factor.

→ *How the risk is managed across other products and/or disease states*
Varies. See table above. REMS in place to address QT prolongation for Tasigna (nilotinib; MG + CP), (b) (4) (dofetilide; deemed REMS not approved; MG+ETASUs). (b) (4) was recently withdrawn from the market. (b) (4) not approved due, in part, to QT prolongation.

- **Size of population**
  MTC is a rare malignancy with approximately 2000 new cases per year in the US.

- **Seriousness of disease**
  Early stage disease can be treated surgically with curative intent and patients known to be at risk for the hereditary forms of the disease often undergo prophylactic thyroidectomy. Not all patients with MTC need immediate therapy. This rare malignancy has a long natural history and patients with distant metastases have a 10-year survival of approximately 40%. Most patients in the vandetanib treatment population will ultimately die of this disease.

- **Expected benefit**
  AstraZeneca are seeking approval of the NDA in patients with unresectable locally advanced or metastatic MTC. (b) (4) There is currently no approved treatment for patients with MTC.

  The primary endpoint from the 3 studies (1 Phase 3, 2 Phase 2) was progression free survival (PFS). Vandetanib demonstrated clear prolongation of PFS compared to placebo, hazard ration 0.35 (95% CI; 0.24-0.53). Because the of the relatively long disease history, the value of PFS is difficult to assess and information on overall survival is not available. It is not known if PFS is clinically meaningful.

- **Expected actual duration of treatment**
  Once vandetanib treatment begins, patients receive 300 mg daily until disease progression. Treatment can continue for months to years.

- **Products affected**
  Vandetanib is a new molecular entity. There are no generic formulations available.

ANALYSIS OF OPTIONS

The goals are to:

- to minimize the risk of sudden death resulting from QT prolongation by educating prescribers about the risk of QT prolongation/sudden death associated with vandetanib and appropriate monitoring; and
- inform patients of the serious risks associated with vandetanib

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(b) (4)

In conjunction with labeling (including a Boxed Warning), the following options have been considered:

1. REMS with Medication Guide (MG) and Communication Plan
2. REMS with MG and ETASU **not** tied to drug distribution
    - HCPs who are specially certified or trained
3. REMS with MG and ETASU tied to drug distribution
    - HCPs who are specially certified or trained
    - Pharmacies that dispense the drug are specially certified to ensure only certified prescribers are prescribing vandetanib
4. REMS with MG and ETASU tied to drug distribution with patient involvement
    - HCPs who are specially certified or trained
    - Pharmacies that dispense the drug are specially certified to ensure only certified prescribers are prescribing vandetanib
    - Documentation of safe use conditions
        - Patient-Prescriber Acknowledgement
        - Drug interaction monitoring

The review team recommends REMS with MG and ETASU tied to drug distribution (Option 3).

Review of all options considered are provided.

1. REMS with MG and Communication Plan

Communication Plan would consist of material educating prescribers about the risks of QT prolongation and sudden death associated with vandetanib and appropriate monitoring. Prescribers complete a short "quiz" online to assess knowledge and understanding.	
Advantages	**Disadvantages**
• Passive route of risk education; least burdensome approach • No impact on drug distribution • Opportunity to inform patients on risk and risk factors in effort to prevent serious adverse event • Assessment would include analysis of HCP and PT knowledge or risks	• No active assurance that prescribers have reviewed materials before prescribing. • No incentive for prescribers to become certified • Difficult to assess impact.
Anticipated Consequences • Not all prescribers will review/receive training. Need to define "success," develop threshold and contingency plan if "success" is not achieved. Percentage of prescribers who received training cannot be the only metric.	

2. REMS with MG and ETASU <u>not</u> tied to drug distribution

ETASU focused on prescriber training. The training would consist of material educating prescribers about the risk of QT prolongation and sudden death with vandetanib and appropriate monitoring. Prescribers complete a short "quiz" online to assess knowledge and understanding. Only those who "passed" would be considered "trained" prescribers.	
Advantages	**Disadvantages**
• No impact on drug distribution • Opportunity to inform patients on risk and risk factors in effort to prevent serious adverse event mandate	• Not very different from Option #1. • From a regulatory standpoint, training fits better under ETASU than CP. o A MG+CP was employed for Xiaflex and the main goals was provide

• Assessment would include analysis of HCP and PT knowledge or risks	appropriate training materials on how to administer Xiaflex properly. • No incentive for prescribers to become certified unless tied to continuing medical education • Difficult to assess impact.
Anticipated Consequences • Not all prescribers will review/receive training. Need to define "success," develop threshold and contingency plan if "success" is not achieved. Percentage of prescribers who received training cannot be the only metric.	

3. REMS with MG and ETASU (prescriber certification) tied to drug distribution

ETASU A/certification would consist of material educating prescribers about the risk of QT prolongation/sudden death and appropriate monitoring. Prescribers complete a short "quiz" online to assess knowledge and understanding. Only those who "passed" would be considered "certified" prescribers. Pharmacies would only accept/dispense prescriptions written by certified prescribers (ETASU B).	
Advantages	**Disadvantages**
• Definitive data that prescribers complete training • Only trained (and hopefully aware) prescribers prescribe vandetanib	• Oncology community is the prescribing group most affected by REMS • Requires another ETASU (pharmacy certification) to ensure that pharmacies know to check for this. Sponsor using specialty pharmacies so this is minimal to no additional burden from the pharmacy perspective.
Anticipated Consequences • Drug would not be dispensed unless written by a certified prescriber. • Treatment delays (both intended and unnecessary) • Negatively impact the number of prescribers who can prescribe, leaving certain patients without access to a drug that may benefit them. • Backlash from oncology community	

4. REMS with MG and ETASU (certification + documentation of safe use conditions) tied to drug distribution

Documentation of safe use conditions and/or required monitoring of some sort were considered. Safe use condition documentation could consist of patient-prescriber acknowledgement (or informed consent) regarding the risks associated with vandetanib. To ensure this was completed for *all* patients, this would require prescriber and pharmacy certification.

Another safe use condition would be to require the specialty pharmacy to keep a medication history on file and review and update the medication list prior to dispensing each prescription in effort to detect and prevent drug interactions. Because the sponsor plans to distribute vandetanib through specialty pharmacies, these pharmacies most likely will not have a list of active medications on file because they do not dispense those medications to the patient. This approach could, but does not require, prescriber certification. It would require pharmacy certification.

Advantages	Disadvantages
• Targets additional risk factors in effort to detect/prevent SAEs • Ensures patients are aware of the risks. Oncology patients are consented before treatment, it is not clear if this drug would have consent in practice.	• Most burdensome approach • Oncology community is the prescribing group most affected by REMS • Requires another ETASU (prescriber and/or pharmacy certification, and documentation of safe use) to ensure that pharmacies know to check for required measures. Sponsor using specialty pharmacies so this is not substantial additional burden for pharmacies.
Anticipated Consequences • Same as #3 above • Additional caused for treatment delays (both intended and unnecessary)	

With regard to required monitoring, the risks do not lend themselves to a definitive monitoring plan to prevent adverse events. For QT prolongation, as stated above, it is not practical to monitor a patient continuously and periodic monitoring may be helpful but is not an absolute mitigation strategy. It would be cumbersome to implement and the value, at this time, does NOT outweigh the burden of enrolling patients and collecting the information.

SUMMARY

Determining the appropriate REMS depends on a number of factors. Given the long natural history for MTC and risk of sudden death associated with vandetanib's impressive effect on QT interval, understanding the risk and appropriate monitoring is important for prescribers.

Comments/Questions for DDOP

1. see marked up REMS draft
2. Goals - how should it read
3. Communication Plan
    a. Professional society interaction (1) j ad, 2) letter to leadership to disseminate 3) annual convention booth – which ones or all and which prof societies
    b. Who to target – "likely to prescribe vandetanib" who treat advanced MTC (medical oncs, endos, surgeons) --
4. Enrollment – attestation points. Too many in my opinion. Divide up, add headers (drug interactions, electrolyte monitoring/repletion, ECG monitoring, dosing)
5. Knowledge assessment – what are the main points you want to drive home, how easy/hard should the questions be, how many questions

Mentioned in REMS/SD	**Submitted**	
Website	No	
HCP Educational Pamphlet	No	
DHCP letter	Yes	
Society letter	Yes	
HCP Enrollment Form	Yes	
Pharmacy Enrollment	Yes	Plan to go with a sp pharm
Knowledge Assessment	Yes	
Slide deck	yes	

Comments/Questions for AZ

1. Educational Materials:
    a. In order to reach as many healthcare providers as possible, we suggest disseminating the DHCP Letter through various media. For example, in addition to hardcopy, the letter could be sent electronically. If you do not choose to us electronic mailings, please provide a rationale for this decision.
    b. State how you plan to identify targeted providers, what databases you plan to access. Provide estimates on the numbers of providers by specialty you plan to target.
    c. We agree that it is appropriate to disseminate the DHCP letter for one year. All other materials should be available for as long as the program continues.
    d. HCP Pamphlet – Page 5, Supporting Document: You state that this pamphlet "will be distributed by AZ field-based personnel during the first discussion of the product with all HCPS visited during the firs year after product launch." Explain why this pamphlet should not be provided at the time of first discussion with a prescriber after the first year.
    e. Professional Society Letter – Page 6, Supporting Document: You state that you will "request that these societies disseminate this information to their respective members an associated medical journal together with the link to the aforementioned website." Do you expect that the societies will publish something in their associated journal?

f. Explain how the slide deck will be used.
g. Website: We recommend that you include a prominent link on the product website's homepage for REMS materials. We remind you that any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a single-click, prominent direct link off the main website that includes REMS-specific materials. This link will direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The REMS-related webpage(s) should not be a means to promote vandetanib or any other AstraZeneca product. Only the separate webpage(s) and/or link will be considered a component of the REMS.
    i. We recommend a single-click, direct, prominent link off the' vandetanib homepage to a REMS landing page. For example, the link could state:

        "Important Safety Information and Risk Evaluation and Mitigation Strategy (REMS)", or "Healthcare Professionals click here for Risk Evaluation and Mitigation Strategy (REMS) information."
    ii. The landing page of the separate REMS link should contain background information on the REMS, as well as safety information, along with the REMS communication materials. .
    iii. We recommend the following language as background information on the REMS landing page:

        A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

        In order for <<SPONSOR NAME>> to communicate certain risks about <<DRUG, SPONSOR NAME>> has worked with the FDA to develop materials to communicate the risks of [list risks; bullet format if multiple]

        The REMS program is designed to inform health care providers and patients about the risks with <<DRUG>>. To learn more about serious risks, read the important safety information provided in this link, including the Medication Guide, and discuss it with your patients.

        The goals of the <<DRUG>> REMS are:

h. Submit for review the web screenshot(s) for the vandetanib REMS.
i. When will the following pieces be submitted:
    i. Website
    ii. HCP pamphlet

2. Explain how a prescriber enrolls, prescribes to a patient, and how the patient gets the drug.
3. Explain how does REMS addresses inpatient use, long-term care, and/or hospice use
4. Explain whether or not the specialty pharmacy will be able to accept electronic prescriptions
5. Knowledge Assessment:
6. Provide Word documents of all materials.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DRISK INTERIM REMS REVIEW

Date: March 10, 2011

To: Robert Justice, MD, Director
Division of Drug Oncology Products (DDOP)

From: Suzanne Robottom, PharmD, Risk Management Analyst, Division of Risk Management (DRISK)

Jodi Duckhorn, MA, Senior Social Science Reviewer (DRISK)

Subject: Interim REMS Review **Comments Set 2**

Drug Name: vandetanib

Application Type/Number: NDA 22-405

Applicant: AstraZeneca

I. Material Reviewed

- Astra Zeneca proposed REMS for vandetanib submitted on February 10 and February 17, 2010.

II. Comments to AstraZeneca

Please be aware that these are preliminary comments. You will receive additional comments as your REMS undergoes further review.

REMS Document

1. See the attached revised REMS document.

Website

1. Explain how the website documents you submitted are related. (b) (4)

(b) (4)

a. We remind you that any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a direct link (with equal prominence to efficacy claims and information) off the main product website that includes REMS-specific materials. This link will direct users to a webpage that describes the REMS program and lists only approved REMS materials. The webpage should not be a means to promote vandetanib or any other Sponsor product. Only this webpage and/or link will be considered a component of the REMS. To this end, we want to ensure what we are reviewing are specific to the REMS (vs what was provided for context). For example:

(b) (4)

(b) (4)

(b) (4)

[redacted]

Slide Deck

1. Revise the slide deck to be consistent with comments and revisions you have received for other materials.
2. Include any voiceover and graphics if you intend to make this a webinar available on the website.

Pharmacy Enrollment Form

1. See the attached revised Pharmacy Enrollment Form.

Knowledge Assessment Questions

1. Organize the questions into 6 categories as follows:
   - Risk
   - Appropriate patient selection
   - Electrolyte monitoring
   - ECG monitoring
   - Drug drug interactions
   - Dosage and administration

   These categories are consistent with the 6 sections in the HCP Educational Pamphlet.
2. Ensure that each category has at least 4 questions. We note there is only one question on drug-drug interactions.
3. Revise the prescriber knowledge assessment (or enrollment test) to include 6 questions (one from each category) and prescribers must get 83% (5 out of 6 questions correct) to become certified.
5. The website interaction flow states, [redacted] (b) (4)

(b) (4)

6. In addition to accessing the knowledge assessment online, ensure you have a process in place to allow prescribers to complete the assessment on paper.
7. Revise each question to reference the prescribing information or the HCP educational pamphlet. For example, “According to the Prescribing Information, ….”
8. When the REMS is approved, the knowledge assessment will be appended to the REMS. Because this information is publicly available, the final document that is attached to the REMS should *not* include the correct answers.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DRISK INTERIM REMS REVIEW

Date: March 31, 2011

To: Robert Justice, MD, Director
Division of Drug Oncology Products (DDOP)

From: Suzanne Robottom, PharmD, Risk Management Analyst,
Division of Risk Management (DRISK)

Subject: Interim REMS Review **Comments Set 3**

Drug Name: vandetanib

Application Type/Number: NDA 22-405

Applicant: AstraZeneca

I. Material Reviewed

- Astra Zeneca proposed REMS for vandetanib submitted on March 22 and March 24 (revised convention panel), 2011.

II. Comments to AstraZeneca

Please be aware that these are preliminary comments. You will receive additional comments as your REMS undergoes further review. We plan to discuss these comments and answer any questions at an upcoming teleconference. During the teleconference, we will discuss the content and timing of your re-submission of these materials.

HCP Education Pamphlet

1. Increase prominence of "vandetanib and risk of QT Prolongation, Torsades de Pointes, and Sudden Death" on the cover page.
2. Page 2 – Unbold the indication. It is not the most important information on the page.
3. Page 3 - Revise the flow chart as follows:
    a. Step 1 - Revise this step [redacted] (b) (4)
    b. Step 2 – Refer to the knowledge assessment as a “training program” given the revised expectations for implementation. Therefore, revise Step 2 to refer to

training program. For example. "Complete the prescriber training program (online or phone)."

i. Review all materials to ensure this change in terms is made uniformly throughout all materials/documents.

c. Step 3 – Revise Step 3 to state [redacted] (b) (4)

d. Increase the prominence of the following statement: "To ENROLL, visit www. Or call 1-800…."

e. We note that the pamphlet contains at least 3 different phone numbers. We recommend referring a prescriber to a single number, if possible.

i. Review all materials to ensure this change in terms is made uniformly throughout all materials/documents.

4. Page 4: Revise the following statement as follows [redacted] (b) (4)

a. Review all materials to ensure this change in terms is made uniformly throughout all materials/documents.

5. Page 6: The checkmark bullets imply a positive action. Overall, the text accompanying the checkmarks in this box calls out patients who should NOT receive vandetanib vs patients that are appropriate. Therefore, we recommend you choose a different graphic.
6. Page 11-15: Delete these pages.

Prescription Referral Form

1. We believe the word [redacted] (b) (4) is confusing. It appears that the purpose of the form is to order/prescribe vandetanib. We recommend revising the title to "prescription order form" or "prescription form" or "vandetanib prescription form" or similar.

Knowledge Assessment

1. As stated above, revise the title of this aspect of the REMS to "training program."
2. Revise each question to reference the prescribing information or the HCP educational pamphlet. For example, "According to the Prescribing Information, …."
3. When the REMS is approved, the knowledge assessment will be appended to the REMS. Because this information is publicly available, the final document that is attached to the REMS should *not* include the correct answers. In your next submission, provide a document that does not contain the correct answers.

Prescriber Enrollment Form

1. In #1, delete reference to [redacted] (b) (4) and state that the prescriber has read the pamphlet OR the slide set.
2. In #1, revise it to state, " I have completed the training program."
3. Bold the section title "Risk of QT prolongation, Torsades de pointes, and Sudden Death."

Pharmacy Enrollment Form

1. No comments.

Slide Set

1. Revise title slide to prominently state "vandetanib and risk of QT prolongation, Torsades de pointes, and Sudden Death."
2. We note that the pamphlet contains at least 3 different phone numbers. We recommend referring a prescriber to a single number, if possible.
    a. Review all materials to ensure this change in terms is made uniformly throughout all materials/documents.
3. Slide 3 - Indent the 2nd, 3rd, and 4th bullets
4. Slide 12, 13,and 14 – Delete these slides.

REMS Website Site

(b) (4)

HCP Home website:

(b) (4)

New Prescriber Enrollment Form

1. Page 4 - Revise "knowledge assessment" on this page and pages 5 through 16.
2. Page 17 - Revise (b) (4) to "agreement."
3. Page 17 - Is an electronic signature necessary?

Convention Panel

(b) (4)

REMS Assessment

- We request the following information be provided for each REMS assessment. (we note that the KAB surveys will not be in the 6 month assessment). These should be incorporated into the REMS Supporting Document.

The REMS assessment plan should include, but is not limited to, the following:

1. With regard to the assessment of the Medication Guide:

An evaluation of patients' understanding of the serious risks of vandetanib

   a. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
   b. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

2. With regard to the assessment of the communication plan:
   a. The date of product launch and the launch of the communication plan
   b. The date(s) of mailing(s) and number of recipients of the Dear Healthcare Provider (DHCP) letter and Dear Professional Society Letter
   c. The number of mailings returned
   d. The sources of the recipient lists
   e. A copy of all documents included in each mailing
   f. The names and dates of any conferences attended by AstraZeneca and where commercial vandetanib product information was displayed

3. With regard to Prescriber Certification:
   a. The number of healthcare providers accessing the training program (during the reporting period and cumulative).
   b. The number of healthcare providers who complete the training program but do not complete enrollment (during the reporting period and cumulative).
   c. The number of healthcare providers enrolled in the Vandetanib REMS (during the reporting period and cumulative) and stratify by prescriber specialty.
   d. A summary of the method prescribers used to enroll (online or phone).
   e. Proportion of prescribers that correctly answer each training program question and stratify by specialty.
   f. The number of enrolled healthcare providers actively prescribing Vandetanib during the reporting period (i.e., have written at least one prescription in the in the time period).
   g. The number of healthcare providers who have ordered/prescribed Vandetanib who were not enrolled (during the reporting period and cumulative).

4. With regard to Pharmacy Certification and distributors:
   a. The number of pharmacies enrolled (during the reporting period and cumulative).
   b. The number of pharmacies ordered/dispensed Vandetanib who were not enrolled.
   c. The number of distributors that distributed Vandetanib who were not enrolled (during the reporting period and cumulative).

5. With regard to Risk of QT prolongation, Torsades de pointes, and sudden death:
    a. An *analysis* of the post-marketing cases for Torsades de pointes or sudden death reported in association with vandetanib to AstraZeneca (during the reporting period and cumulative) with attention to possible factors that prolonged the QTc (e.g., interacting medication initiated, change in patient's health status, failure to adjust dose, lack of ECG monitoring, lack of electrolyte monitoring, etc.).
    b. The number of patients who were dispensed Vandetanib (during the reporting period and cumulative).
    c. An evaluation of healthcare providers' understanding of the serious risk of vandetanib.
6. Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed.
7. Specification of measures that would be taken to increase awareness if surveys of patients or healthcare providers indicate that awareness is not adequate.
8. Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

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/s/

SUZANNE C BERKMAN ROBOTTOM
04/06/2011

CLAUDIA B KARWOSKI
04/06/2011
concur

Risk Evaluation and Mitigation (REMS Memorandum)

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ONCOLOGY PRODUCTS
DIVISION OF DRUG ONCOLOGY PRODUCTS

NDA #: 022405
Products: vandetanib tablets, 100 mg and 300 mg
SPONSOR: AstraZeneca
FROM: Robert Justice, M.D.
DATE: December 27, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for vandetanib to ensure that the benefits of the drug outweigh the risks of QT prolongation and torsades de pointes. In reaching this determination, we considered the following:

A. Vandetanib is indicated for the treatment of unresectable, locally advanced or metastatic medullary thyroid cancer (MTC). According to the American Cancer Society, MTC accounts for approximately 4% of all thyroid cancer which translates to an estimated 1,800 patients being diagnosed with MTC and 68 patients dying from MTC in 2010.

B. Unresectable MTC is a life threatening disease.

C. Clinical studies have shown that vandetanib improves progression-free survival in patients with unresectable MTC.

D. Vandetanib is an important therapeutic option in the treatment of those patients who cannot benefit from surgery for MTC. Duration of treatment with vandetanib is expected to be chronic, until there is evidence of disease progression.

E. Prolongation of the QT interval with associated outcomes of Torsades de Pointes and sudden death has been reported in clinical studies of vandetanib. At the dose of 300

mg, vandetanib is associated with substantial (mean effect over 30 ms) and concentration-dependent QTc prolongation, and the QTc prolongation is sustained over time. In 231 MTC patients receiving vandetanib 300mg once daily 25.5% of the patients in the vandetanib 300 mg arm experienced greater than 60 ms increase in the QTc interval. In the cumulative clinical experience with vandetanib, there has been a total of 2 confirmed cases of Torsades de Pointes at the 300 mg dose.

F. Vandetanib is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for vandetanib. FDA has determined that vandetanib poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of vandetanib. FDA has determined that vandetanib is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use vandetanib, and that vandetanib is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be a Medication Guide, a communication plan, elements to assure safe use (healthcare providers who prescribe the drug are specially certified or trained [section 505-1(f)(3)(A)] and pharmacies, practitioners, or health care settings that dispense the drug are specially certified [section 505-1(f)(3)(B)]), an implementation system, and a timetable for submission of assessments of the REMS.

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/s/

LISA M SKARUPA
01/21/2011

ROBERT L JUSTICE
01/21/2011