

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022405Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	<i>electronic stamp date</i>
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 22405/S000
Applicant	AstraZeneca Pharmaceuticals, LP
Date of Submission	July 7, 2010
PDUFA Goal Date	April 7, 2011
Proprietary Name / Established (USAN) names	Proprietary name is not yet approved/vandetanib
Dosage forms / Strength	100 mg, 300 mg tablets
Proposed Indication(s)	Vandetanib is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease
Recommended:	<i>Approval</i>

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Geoffrey Kim (efficacy), Katherine DeLorenzo (safety)
Statistical Review	Somesh Chattopadhyay, Shenghui Tang
Pharmacology Toxicology Review	Brenda Gehrke, Robert Dorsam, Leigh Verbois
CMC Review/OBP Review	Wendy Wilson-Lee, Debasis Ghosh, John Duan
Microbiology Review	N/A
Clinical Pharmacology Review	Pengfei Song, Young Jin Moon, Marathe Anshu
DDMAC	James Dvorsky
DSI	Lauren Iacono-Conners
CDTL Review	Ellen Maher
OSE/DMEPA	Denise Baugh
OSE/DDRE	N/A
OSE/DRISK	Lotonia Ford
Other: REMS team	Suzanne Berkman Robottom, Joyce Weaver
Ophthalmology Consult	William Boyd

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DDRE= Division of Drug Risk Evaluation
 DRISK=Division of Risk Management

1. Introduction

Vandetanib is a multi-tyrosine kinase inhibitor, which inhibits various growth factor receptors and the RET oncogene. It is a potent inhibitor of VEGFR2. In medullary thyroid cancer (MTC), vandetanib is able to work through RET, EGFR, and VEGFR2. EGFR is present on the cell surface of 13% of MTCs while VEGFR2 has been found on vessels associated with MTCs.

MTC is a rare malignancy of the parafollicular C-cells of the thyroid, which occurs in sporadic and hereditary forms. Both hereditary and sporadic disease are associated with an activating mutation in the RET proto-oncogene. RET mutations occur in most hereditary forms and in the tumors of 50-80% of patients with the sporadic form of the disease.

Early stage disease can be treated surgically with curative intent and patients known to be at risk for the hereditary forms often undergo prophylactic thyroidectomy; however, there are no approved drugs for the treatment of MTC. In patients with distant metastases, 10-year survival is approximately 40%. It is estimated that there were 1800 new cases of MTC in the US in 2010.

AstraZeneca has submitted an NDA for vandetanib in patients with unresectable locally advanced or metastatic MTC. A single randomized Phase 3 study was submitted as the registration trial for this application. The application was also supported by 2 single arm Phase 2 studies in patients with MTC.

2. Clinical/Statistical- Efficacy

The pivotal trial in support of this application is study 1 as described below.

Study 1: This study randomized 331 patients with unresectable locally advanced or metastatic MTC in a 2:1 ratio to vandetanib 300 mg (n=231) or placebo (n=100) daily. Measurable disease was required and included patients with hereditary and sporadic forms of MTC. There were no requirements concerning prior treatment or the pace of the disease. Patients were treated until investigator-determined progression.

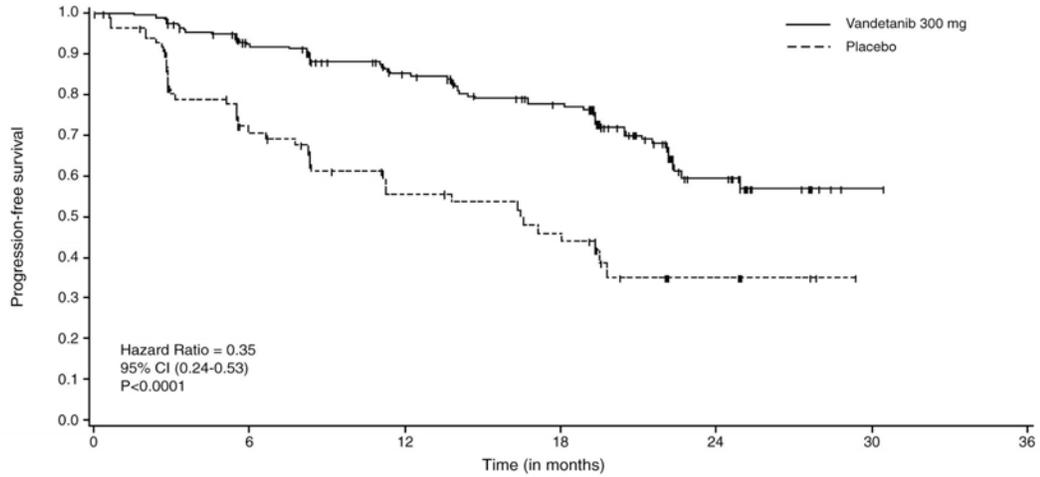
As described in Dr. Justice's Summary Review and the package insert, the primary endpoint was demonstration of improvement in progression-free survival (PFS) with vandetanib compared to placebo. Other endpoints included evaluation of overall survival (OS) and overall objective response rate (ORR). Centralized, independent blinded review of the imaging data was used in the assessment of PFS and ORR. Upon objective disease progression based on the investigator's assessment, patients were discontinued from blinded study treatment and given the option to receive open-label vandetanib. Nineteen percent (44/231) of the patients initially randomized to vandetanib opted to receive open-label vandetanib after disease progression, and 58% (58/100) of the patients initially randomized to placebo opted to receive open-label vandetanib after disease progression.

The result of the PFS analysis, based on the central review RECIST assessment, showed a statistically significant improvement in PFS for patients randomized to vandetanib (Hazard Ratio = 0.35; 95% Confidence Interval (CI) = 0.24-0.53; $p < 0.0001$). Analyses in the subgroups of patients who were symptomatic or had progressed within 6 months prior to their enrollment showed similar PFS results (HR

= 0.31 95% CI: 0.19, 0.53 for symptomatic patients; HR = 0.41 95% CI: 0.25, 0.66 for patients who had progressed within 6 months prior to enrollment).

At the time of the primary analysis of PFS, 15% of the patients had died and there was no significant difference in OS between the two treatment groups. The overall ORR for patients randomized to vandetanib was 44% compared to 1% for patients randomized to placebo. All objective responses were partial responses.

Figure 1- Progression Free Survival



n at months	0	6	12	18	24	30	36
Vandetanib 300 mg	231	173	145	118	33	1	0
Placebo	100	47	30	24	6	0	0

Table 1: Summary of key efficacy findings

PROGRESSION-FREE SURVIVAL	N ^a	Median PFS (95% CI)	HR ^b	95% CI	p-value ^c
Vandetanib 300 mg	59/231 (26%)	Not reached (22.6 months, NE ^[d])	0.35	0.24, 0.53	<0.0001
Placebo	41/100 (41%)	16.4 months (8.3, 19.7)			

[a] N = Number of events/number of randomized patients
 [b] HR= Hazard Ratio, Cox Proportional Hazards Model
 [c] Logrank test
 [d] NE = non-estimatable

Supportive Studies

Two single arm Phase 2 studies have been conducted in patients with hereditary MTC.

Study 2

Study 2 is an open-label, two-stage, phase 2 study (N=30) to evaluate the efficacy and tolerability of ZD6474 (300 mg) in patients with locally advanced or metastatic hereditary MTC.

In general, the baseline disease characteristics of patients in Study 2 were more favorable than those in Study 1. The table below shows the RR by investigator (RECIST criteria without a lower limit for nodal size) and IRC (modified RECIST criteria as in Study 1). While the investigator and IRC RR are similar, only 2 of the 6 patients with an INV response were considered responders by the IRC.

Table 2: Response Rate Study 2 (Data Cutoff 2-22-08)		
Response Rate (CR+PR)	Vandetanib 300 mg N = 30	Median Duration of Response (range)
Investigator Response	6 (20.0%)	311 days (137-850)
IRC Response	5 (16.7%)	500 days (337-980)

Study 3

Study 3 is a phase 2, open-label study (N=19) to assess the efficacy and tolerability of ZD6474 (ZACTIMA™) 100 mg monotherapy in subjects with locally advanced or metastatic hereditary MTC. In general, baseline disease characteristics of patients in Study 3 were more favorable than those in Study 1. The table below shows the RR by investigator using modified RECIST criteria (as in Study 1). On progression, patients thought to be benefitting could receive vandetanib 300 mg. Four patients choose this option; 3 had SD and 1 had PD.

Table 3: Response Rate Study 3 (Data Cutoff 1-31-08)		
Response Rate (CR+PR)	Vandetanib 100 mg N = 19	Median Duration of Response (range)
Investigator Response	3 (15.8%)	168 days (158-245)

Note that while the investigator RR in patients receiving vandetanib 100 mg in Study 3 appears to be lower than the RR in Study 1 (15.8% vs. 39.0%) it is similar to the investigator RR in Study 2 (15.8% vs. 20.0%). Study 2 administered vandetanib 300 mg.

3. Safety

As in Dr. Justice's Summary Review, adverse reactions are described in the agreed upon package insert as following:

The most commonly reported adverse drug reactions (>20%) have been diarrhea, rash, acne, nausea, hypertension, headache, fatigue, decreased appetite, and abdominal pain. The most common laboratory abnormalities (>20%) were decreased calcium, increased ALT, and decreased glucose.

Table 4 - Adverse Reactions in >10% of Patients on Vandetanib During Randomized Treatment

Preferred Term	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%)
Rash ¹	123 (53%)	11 (5%)	12 (12%)	0
Dermatitis Acneiform/Acne	81 (35%)	2 (1%)	7 (7%)	0
Nausea	77 (33%)	2 (1%)	16 (16%)	0
Hypertension/Hypertensive Crisis/Accelerated hypertension	76 (33%)	20 (9%)	5 (5%)	1 (1%)
Headache	59 (26%)	2 (1%)	9 (9%)	0
Fatigue	55 (24%)	13 (6%)	23 (23%)	1 (1%)
Decreased Appetite	49 (21%)	10 (4%)	12 (12%)	0
Abdominal Pain ²	48 (21%)	6 (3%)	11 (11%)	0
Dry Skin	35 (15%)	0	5 (5%)	0
Vomiting	34 (15%)	2 (1%)	7 (7%)	0
Asthenia	34 (15%)	6 (3%)	11 (11%)	1 (1%)
ECG QT Prolonged ³	33 (14%)	18 (8%)	1 (1%)	1 (1%)
Photosensitivity Reaction	31 (13%)	4 (2%)	0	0
Insomnia	30 (13%)	0	10 (10%)	0
Nasopharyngitis	26 (11%)	0	9 (9%)	0
Dyspepsia	25 (11%)	0	4 (4%)	0
Hypocalcemia	25 (11%)	4 (2%)	3 (3%)	0
Cough	25 (11%)	0	10 (10%)	0
Pruritus	25 (11%)	3 (1%)	4 (4%)	0
Weight Decreased	24 (10%)	2 (1%)	9 (9%)	0
Proteinuria	23 (10%)	0	2 (2%)	0
Depression	22 (10%)	4 (2%)	3 (3%)	0

¹ Includes rash, rash erythematous, generalized, macular, maculo-papular, papular, pruritic, exfoliative, dermatitis, dermatitis bullous, generalized erythema and eczema.

² Includes abdominal pain, abdominal pain upper, lower abdominal pain and abdominal discomfort

³ 69% had QT prolongation >450ms and 7% had QT prolongation >500ms by ECG using Fridericia correction.

Adverse reactions resulting in death in patients receiving vandetanib (N=5) were respiratory failure, respiratory arrest, aspiration pneumonia, cardiac failure with arrhythmia, and sepsis. Adverse reactions resulting in death in patients receiving placebo were gastrointestinal hemorrhage (1%) and gastroenteritis (1%). In addition, there was one sudden death and one death from cardiopulmonary arrest, in patients receiving vandetanib after data cut-off. Causes of discontinuation in vandetanib-treated patients in >1 patient included asthenia, fatigue, rash, arthralgia, diarrhea, hypertension, prolonged QT interval, increase in creatinine and pyrexia. Serious adverse events in vandetanib-treated patients in >2% of patients included diarrhea, pneumonia, and hypertension. Clinically important uncommon adverse drug reactions in patients who received vandetanib versus patients who received placebo included pancreatitis (0.4% vs. 0%) and heart failure (0.9% vs. 0%). In the integrated summary of safety database, the most common cause of death in patients who received vandetanib was pneumonia.

The incidence of Grade 1-2 bleeding events was 14% in patients receiving vandetanib compared with 7% on placebo in the randomized portion of the MTC study. The incidence was similar in the 300 mg monotherapy safety program with a 13% incidence.

Blurred vision was more common in patients who received vandetanib versus patients who received placebo for MTC (9% vs. 1%, respectively). Scheduled slit lamp examinations have revealed corneal opacities (vortex keratopathies) in treated patients, which can lead to halos and decreased visual acuity. It is unknown if this will improve after discontinuation. Ophthalmologic examination, including slit lamp, is recommended in patients who report visual changes. If a patient has blurred vision, do not drive or operate machinery.

For laboratory abnormalities, alanine aminotransferase elevations occurred in 51% of patients on vandetanib in the randomized MTC study. Grade 3-4 ALT elevations were seen in 2% of patients and no patients had a concomitant increase in bilirubin. Elevations in ALT have resulted in temporary discontinuation of vandetanib. However, 16 of 22 patients with a grade 2 elevation in ALT continued 300 mg vandetanib. Seven patients who continued vandetanib had a normal ALT within 6 months. In the protocol, ALT was monitored every 3 months and more frequently as indicated.

QT Prolongation and Risk Evaluation and Mitigation Strategy (REMS)

The major safety concern that led to a boxed warning, a contraindication for patients with congenital long QT syndrome, a warning and precaution, and a REMS with an ETASU is the potential for vandetanib to prolong the QT interval. The following is an excerpt from the agreed upon package insert:

In 231 MTC 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. Based on the exposure-response relationship, 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). In addition, 36% of patients experienced greater than 60 ms increase in Δ QTcF and 4.3% of patients had QTcF greater than 500 ms. Cases of Torsades de pointes and sudden death have been reported.

The potential for QT prolongation is concerning considering the median plasma half-life of vandetanib is 19 days and patients who present with metastatic disease have a relatively long survival. Therefore, a REMS is required to ensure that prescribers are aware of these risks and are aware of the recommended ECG and electrolyte monitoring, dose interruptions, and dose modifications that are intended to mitigate these risks.

Other warnings and precautions include severe skin reactions (including Stevens-Johnson syndrome), interstitial lung disease, serious hemorrhagic events, heart failure, diarrhea which could result in electrolyte abnormalities, hypothyroidism, hypertension, reversible posterior leukoencephalopathy, drug interactions with strong CYP3A4 inducers, the risks of using vandetanib with other drugs that prolong the QT interval, risks of use in patients with renal and hepatic insufficiency and in pregnant patients.

4. Other Discipline Reviews

There are no other outstanding issues that preclude approval from other disciplines and a summary of other discipline reviews is below.

CMC/Device

CMC reviewers recommended approval of vandetanib 100 mg and 300 mg tablets with resolution of CMC issues and acceptable facility inspections. ONDQA recommended a 36 month expiry of this drug product when stored in the commercial packaging at controlled room temperature.

Nonclinical Pharmacology/Toxicology

The nonclinical review team recommended approval stating that nonclinical studies submitted to this NDA provided sufficient information to support the use of vandetanib in the treatment of unresectable locally advanced or metastatic MTC. However, they recommended that carcinogenicity studies be conducted because of the relatively long expected survival of the proposed patient population. Results of embryo-fetal development studies in the rat, showed that vandetanib is embryotoxic, fetotoxic, and teratogenic to rats at exposures equivalent to or lower than those expected at the recommended dose of 300 mg/day. The reproductive and developmental toxicology studies suggest that administration of vandetanib may also impair fertility. Vandetanib will be assigned Pregnancy Category D.

Clinical Pharmacology/Biopharmaceutics

According to the Clinical Pharmacology review, there is no clear exposure-response relationship for the primary endpoint of PFS. Exploratory analyses of PFS in patients with dose reductions of 200 mg or 100 mg suggested that lower doses might be as effective but less toxic than the recommended dose of 300 mg. A dose reduction to 200 mg was recommended for patients with moderate or severe renal impairment. Use in patients with moderate to severe hepatic impairment was not recommended because of limited data. In addition, strong CYP3A4 inducers should be avoided because rifampicin decreased drug exposure by 48%.

The application is acceptable from a clinical pharmacology perspective and there will be a postmarketing requirement to conduct a trial to explore alternative doses and/or dosage regimens that will reduce the toxicity profile but maintain the efficacy of the 300 mg dose.

5. Other Regulatory Issues

Pediatrics: A pediatric waiver was granted by the Pediatric Review Committee based on vandetanib's orphan drug status.

Advisory Committee Meeting: This application was presented at the December 2, 2010 Oncologic Drugs Advisory Committee (ODAC). Committee members agreed that treatment with vandetanib is not indicated in patients with low burden or asymptomatic disease and agreed with modifying the indication to include only patients with progressive, symptomatic MTC.

In addition, the committee voted 10 to 0 in favor of additional studies to explore alternative doses and dose scheduling.

Labeling

Proprietary name: This application will be approved without a proprietary name.

Labeling: All major issues have been resolved.

6. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Approval

Risk Benefit Assessment

There is no approved therapy for patients with unresectable locally advanced or metastatic MTC. Vandetanib improved PFS in the overall population (HR=0.35; 95% CI 0.24, 0.53; p<0.0001) from a median of 16.4 months with placebo to a minimum of 22.6 months (lower bound of the 95% CI, median not reached) with vandetanib. The PFS finding is supported by an ORR of 44% in the vandetanib arm and 1% in the placebo arm. At the time of the PFS analysis only 15% of patients had died and there was no significant difference in OS.

The major safety concern is the potential for QT prolongation, torsades de pointes, and sudden death. The most common adverse reactions (>20%) were diarrhea, rash, acne, nausea, hypertension, headache, fatigue, decreased appetite, and abdominal pain. The most common laboratory abnormalities (>20%) were decreased calcium, increased ALT, and decreased glucose. Hypocalcemia and electrolyte abnormalities caused by diarrhea can increase the risk for QT prolongation. In addition, because of the drug's long half-life, patients with QT prolongation may be at risk for torsades de pointes and sudden death for a prolonged period of time. These risks may be mitigated if ECG's and serum potassium, calcium, and magnesium are monitored closely and appropriate corrective action is taken.

The benefits and risks of vandetanib were discussed in the Division Director's Summary Review, the Clinical and CDTL Reviews and at the ODAC. ODAC and the clinical reviewers found the risk-benefit assessment to be acceptable in a subgroup of patients with symptomatic or progressive disease. In conclusion, I concur with Dr. Justice's assessment in his summary review as well as the review team's recommendation for approval.

Recommendation for Postmarketing Risk Evaluation and Management Strategies: A REMS is required to ensure safe use of vandetanib.

Recommendation for other Postmarketing Requirements and Commitments: Please refer to the action letter.

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/s/

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04/05/2011

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04/05/2011