CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022405Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	April 1, 2011
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 022405
Applicant Name	AstraZeneca Pharmaceuticals/IPR Pharmaceuticals
Date of Submission	July 7, 2010
PDUFA Goal Date	April 7, 2011
Proprietary Name / **Established (USAN) Name**	Proprietary name is not yet approved/ vandetanib
Dosage Forms / Strength	100 mg and 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.
Action/Recommended Action for NME:	*Approval*

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
Opthalmology 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
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This new drug application for vandetanib for the treatment of medullary thyroid cancer was submitted on 7/7/10. The PDUFA date was extended to 4/7/11 because of a major amendment. This review will summarize the results of the single randomized trial submitted in support of the application and the recommendations of each review discipline.

2. Background

The following background information is summarized from the Clinical Review. Medullary thyroid cancer (MTC) is a rare tumor of the thyroid which arises from the parafollicular C cells. It is estimated that there were 1800 new cases in the US in 2010. About 75% are sporadic and about 25% are associated with the disorder multiple endocrine neoplasia type 2 (MEN2). Mutations in the RET proto-oncogene occur in more than 90% of patients with MEN2A and familial MTC and in 40-50% of patients with sporadic MTC. The prognosis for patients with localized disease that is surgically resected is excellent (~95% at 10 years). Patients with metastatic disease at diagnosis have an estimated 10 year survival of 40%. No drugs are approved for the treatment of medullary thyroid cancer.

Vandetanib is a kinase inhibitor with *in vitro* activity against multiple tyrosine kinases including EFGR, VEGFR, RET, BRK, TIE2, and members of the EPH receptor kinase and Src tyrosine kinase families. In mouse models, vandetanib reduced tumor cell growth and metastasis.

3. CMC/Device

Based on the satisfactory resolution of CMC issues and the acceptable facility inspections recommendation, the CMC reviewers recommended approval of the 100 mg and 300 mg tablets in their memo of 12/23/10. The ONDQA Division Director review of 3/22/11 recommended approval from a Chemistry, Manufacturing and Controls standpoint and recommended granting a 36 month expiry for both strengths of this drug product when stored in the commercial packaging at controlled room temperature; 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF).

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding

CMC issues except for approval of an acceptable tradename. However, that does not preclude approval of vandetanib without a tradename.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review of 12/10/10 recommended approval and stated that the non-clinical studies submitted to this NDA provided sufficient information to support the use of vandetanib in the treatment of unresectable locally advanced or metastatic medullary thyroid cancer. However, the review recommended that carcinogenicity studies be conducted because of the relatively long expected survival of the proposed patient population. The secondary and tertiary reviewers concurred.

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval. Because there are no drugs approved for the treatment of medullary thyroid cancer, the carcinogenicity studies should be postmarketing requirements.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review of 12/8/10 noted that no clear exposure-response relationship could be identified 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 review concluded that the application was acceptable from a clinical pharmacology perspective, provided that agreement is reached on labeling and 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.

The summary of the QT-IRT review noted that "Vandetanib caused substantial and sustained QTc prolongation, Torsades de Pointes, and sudden death. Even intensive ECG monitoring does not mitigate the risk of serious ventricular arrhythmia and sudden death. Given the long $t_{1/2}$ of the drug (19 days), withdrawal, dose interruption or dose-reduction due to QT prolongation still places the patient at increased risk for a prolonged period of time until the drug clears. The Interdisciplinary Review Team (IRT) deferred the risk-benefit considerations pertaining to drug approval to the review division."

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers and the concerns raised by the QT-IRT team. A randomized trial comparing 150 mg

to 300 mg will be conducted as a postmarketing requirement. In addition, as discussed below in section 7, a REMS with an ETASU will be required to help mitigate this risk.

6. Clinical Microbiology

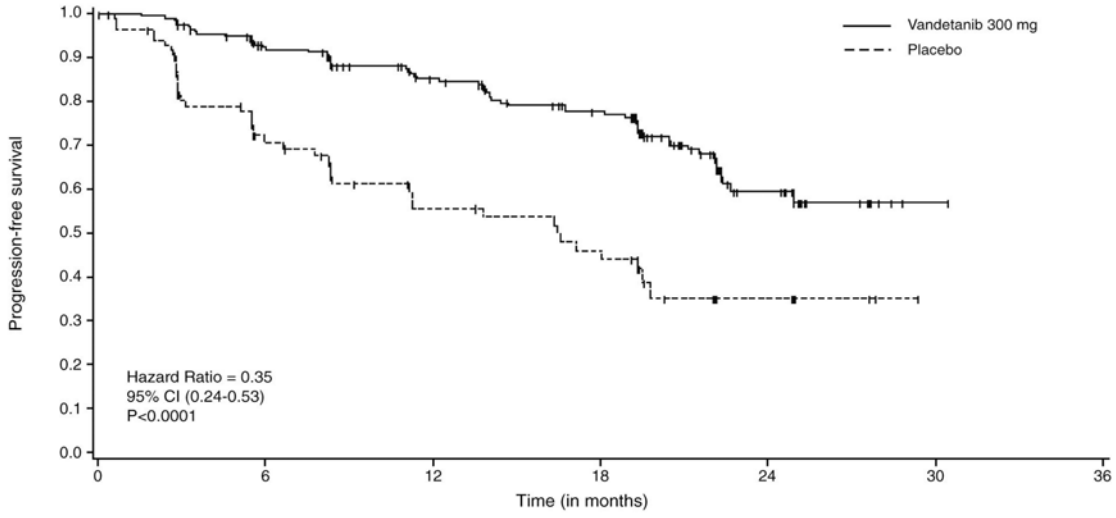
Not applicable.

7. Clinical/Statistical-Efficacy

The following summary of the design and efficacy results of the single randomized study is from the agreed upon package insert.

> A double-blind, placebo-controlled study randomized patients with unresectable locally advanced or metastatic medullary thyroid cancer to vandetanib 300 mg (n=231) versus Placebo (n=100).
>
> The primary objective was demonstration of improvement in progression-free survival (PFS) with vandetanib compared to placebo. Other endpoints included evaluation of overall survival 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 overall survival between the two treatment groups. The overall objective response rate (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 3: 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

The final Clinical Review of 3/24/11 recommended approval and provided the following risk:benefit assessment.

> The recommendation for approval is based on the single, randomized clinical trial in which vandetanib showed a statistically significant progression free survival advantage compared to placebo in patients with locally advanced or metastatic medullary thyroid cancer (MTC).
>
> The single clinical trial enrolled 331 patients with locally advanced or metastatic MTC. The hazard ratio was 0.35 (95% CI 0.24-0.53); p<0.0001, favoring vandetanib. The median progression free survival (PFS) for vandetanib was not yet reached. There were deaths due to toxicity observed on the vandetanib arm in the randomized trial as well as the cumulative clinical experience with vandetanib. Fifty-five percent (55%) of the patients on the vandetanib arm experienced grade 3 or 4 adverse events. Patients receiving vandetanib experienced a mean prolongation of their QT interval of 35 ms, and sudden death and torsades des pointes have been observed with vandetanib. These risks are outweighed by

> the marked improvement in PFS. However, a Risk Evaluation and Mitigation Strategy (REMS) will be used to decrease the risk of vandetanib.
>
> MTC, even in the metastatic setting, has a relatively long survival time. Due to the toxicity profile of vandetanib, the application was presented at the December 2, 2010 Oncologic Drugs Advisory Committee. The members of the committee were asked to discuss whether the indication should be limited to patients with progressive, symptomatic medullary thyroid cancer and to comment on whether there are any other subgroups that may be appropriate for treatment with vandetanib in light of the risk-benefit profile. All of the committee members agreed that treatment is not indicated in patients with a low burden or asymptomatic disease. The majority of the committee members agreed with modifying the indication to those with progressive, symptomatic MTC. The proposed patient population has no treatment options which offer a progression free survival prolongation and the robust results demonstrated by vandetanib would provide a new treatment option for these patients.

The Statistical Review and Evaluation of 12/15/10 confirmed the statistically significant improvement in PFS with vandetanib compared to placebo. The review concluded with "The judgment of meaningulness of the improvement in PFS in light of the toxicities and lack of significant improvement in OS is deferred to the clinical review team." The Statistical Team Leader memo of 12/16/10 concurred with the recommendation.

8. Safety

Adverse reactions are described in the following excerpt from the agreed upon package insert.

> 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 1 - 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 medullary thyroid cancer (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 medullary thyroid cancer (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.

Table 2 provides the frequency and severity of laboratory abnormalities reported for patients with medullary thyroid cancer receiving randomized treatment with vandetanib or placebo.

Table 2 - Laboratory Abnormalities in Patients with MTC

Laboratory Parameter	**Vandetanib 300 mg N = 231**		**Placebo N = 99**	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3-4**
Chemistries				
Calcium Decreased	132 (57%)	13 (6%)	25 (25%)	3 (3%)
ALT Increased	118 (51%)	4 (2%)	19 (19%)	0
Glucose Decreased	55 (24%)	0	7 (7%)	1 (1%)
Creatinine Increased	38 (16%)	0	1 (1%)	0
Bilirubin Increased	29 (13%)	0	17 (17%)	0
Magnesium Decreased	17 (7%)	1 (<1%)	2 (2%)	0
Calcium Increased	16 (7%)	2 (1%)	9 (9%)	1 (1%)
Potassium Decreased	15 (6%)	1 (<1%)	3 (3%)	0
Potassium Increased	13 (6%)	1 (<1%)	4 (4%)	2 (2%)
Glucose Increased	12 (5%)	4 (2%)	7 (7%)	0
Magnesium Increased	6 (3%)	0	4 (4%)	0
Hematologic				
WBC Decreased	45 (19%)	0	25 (25%)	0
Hemoglobin Decreased	31 (13%)	1 (<1%)	19 (19%)	2 (2%)
Neutrophils Decreased	21 (10%)	1 (<1%)	5 (5%)	2 (2%)
Platelets Decreased	18 (9%)	0	3 (3%)	0

Alanine aminotransferase elevations occurred in 51% of patients on vandetanib in the randomized medullary thyroid cancer (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.

The major safety concern that led to a boxed warning, a contraindication for patients with congenital long QT syndrome, a warnings and precaution, and a REMS with an ETASU is the potential for vandetanib to prolong the QT interval. The following excerpt from section 12.4 of the agreed upon package insert summarizes the QT evaluation result.

> 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. Based on the exposure-response relationship, the mean (90% CI) QTcF change from baseline (ΔQTcF) was 35 (33-36) ms for the 300-mg dose. The ΔQTcF remained above 30 ms for the duration of the trial (up to 2 years). In addition, 36% of patients experienced greater than 60 ms increase in ΔQTcF and 4.3% of patients had QTcF greater than 500 ms. Cases of Torsades de pointes and sudden death have been reported.

Since the median plasma half-life of vandetanib is 19 days, this potential for QT prolongation is even more concerning. In addition, as noted in the background section, even patients who present with metastatic disease have a relatively long survival compared with most metastatic cancers. This led to the Vandetanib REMS program which is intended to ensure that prescribers are aware of this risk and the recommended ECG and electrolyte monitoring and dose interruptions and modifications that are intended to mitigate this risk.

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.

9. Advisory Committee Meeting

As noted in section 7, the application was discussed at the 12/2/10 meeting of the Oncologic Drugs Advisory Committee. The following summary of the meeting is from the summary minutes at
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM239356.pdf

> 1. DISCUSS: The proposed indication for vandetanib is for the treatment of unresectable, locally advanced, or metastatic medullary thyroid cancer. Given the substantial toxicity observed with vandetanib and the long natural history of the disease, please discuss whether the indication should be limited to patients with progressive, symptomatic medullary thyroid cancer. Please comment on whether there are any other subgroups that may be appropriate for treatment with vandetanib in light of the risk-benefit profile.
>
> *There was not an overall consensus among the members: some felt that the labeling for the indication should be general and not limiting. They indicated that the physicians treating these patients have the knowledge and expertise necessary to appropriately prescribe vandetanib; their hands should not be tied by restrictive labeling. Others felt that more restrictive labeling should be used but not so restrictive as to prevent access to those who need vandetanib. Several members also recommended that educational efforts towards physicians be made by the sponsor regarding the use of vandetanib.*

Some committee members encouraged the sponsor to create a database and track patients for resistance outcomes and RET mutation status. It was also mentioned that data should be gathered to determine whether there are differences in adverse effects when vandetanib is prescribed by oncologists versus endocrinologists; this recommendation was made because some believe that oncologists monitor adverse effects for oncology products frequently whereas it was felt that endocrinologists may not be used to monitoring as frequently.

2. **VOTE:** If there is a population in which the risk-benefit profile is acceptable, should additional doses of vandetanib be evaluated as a post-marketing requirement to determine the optimal dose? If yes, please discuss potential study designs.

Vote: Yes=10 No = 0 Abstain = 0

Members felt that additional doses of vandetanib should be evaluated as a post-marketing requirement to determine the optimal dose. Members disagreed over whether these studies should be conducted in medullary thyroid cancer patients or patients with other tumor types in which vandetanib may be used. Members felt that there was a signal of activity at a lower dose level than that studied and that a lower dose level should be studied further as having a lower dose could also decrease the toxicity profile. It was also recommended that the dosage schedule be studied further. The current schedule is for vandetanib to given daily. Based on the half-life of vandetanib, some members questioned whether the drug could be given less frequently which may also decrease toxicity. It was also noted that steady state levels should be studied further as steady state levels may be reached at a lower dose without decreasing effectiveness.

10. Pediatrics

Not applicable. Vandetanib has orphan drug exclusivity for this indication.

11. Other Relevant Regulatory Issues

The only outstanding regulatory issue is the finalization of REMS program.

12. Labeling

- Proprietary name: The originally proposed proprietary name was not approved by DMEPA. Another proprietary name is under review. However, this application will be approved without a proprietary name.
- Physician labeling: Agreement was reached on the physician labeling.
- Patient labeling/Medication guide: A Medication Guide is required as part of the REMS.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval pending agreement on the final details of the REMS program.

- Risk Benefit Assessment

  There is no approved therapy for patients with unresectable locally advanced or metastatic medullary thyroid cancer. Patients with symptomatic or progressive medullary thyroid cancer particularly need treatment options. Vandetanib improved progression-free survival 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). The results were similar in exploratory analyses of subgroups of patients who were symptomatic (HR = 0.31 95% CI: 0.19, 0.53) or who had progressive disease within 6 months prior to enrollment (HR = 0.41 95% CI: 0.25, 0.66). The PFS finding is supported by an objective response rate 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 overall survival.

  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 were discussed in the Clinical and CDTL Reviews and at the Oncologic Drugs Advisory Committee. ODAC and the clinical reviewers found the risk benefit assessment to be acceptable in a subgroup of patients with symptomatic or progressive disease. I concur with the clinical team's assessment that the risk benefit assessment is favorable in the subgroup of patients with symptomatic or progressive disease if a REMS with an ETASU is in place.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  The Vandetanib REMS program is intended to mitigate the risk of torsades de pointes and sudden death due to QT prolongation by ensuring that prescribers are aware of the

risks and risk factors, the recommended ECG and electrolyte monitoring, and the dose interruptions and modifications that are intended to mitigate the risks.

- Recommendation for other Postmarketing Requirements and Commitments

  The first two PMR's are studies intended to evaluate the unexpected serous risk of carcinogenicity. The third and fourth PMR's are clinical trials intended to assess a known serious risk of vortex keratopathy and corneal stromal changes, to assess signals of excessive toxicity at the studied dose and heart failure, and to identify an unexpected, serious risk of an adverse effect on overall survival.

  1. To evaluate the potential for a serious risk of carcinogenicity, conduct a long-term (2 year) rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for a Special Protocol Assessment prior to initiating the study.

  2. To evaluate the potential for a serious risk of carcinogenicity, conduct a rodent carcinogenicity study in the mouse. Submit the carcinogenicity protocol for a Special Protocol Assessment prior to initiating the study.

  3. Conduct a randomized dose-finding trial in which patients with progressive or symptomatic medullary thyroid cancer will be randomized to vandetanib 300 mg or 150 mg daily. Safety assessments will include evaluation of vortex keratopathy and corneal stromal changes, with ophthalmology examination every 6 months with corneal photographs of abnormalities. Safety assessments will also include evaluation of heart failure using serial echocardiograms in all patients. A primary endpoint will include overall response rate.

  4. Submit the results of the final analysis of overall survival data from the randomized clinical trial of vandetanib 300 mg vs. placebo in medullary thyroid cancer (Study 58).

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/s/

ROBERT L JUSTICE
04/01/2011