Vandetanib for the Treatment of Symptomatic or Progressive Medullary Thyroid Cancer in Patients with Unresectable Locally Advanced or Metastatic Disease: U.S. Food and Drug Administration Drug Approval Summary


Abstract
On April 6, 2011, the U.S. Food and Drug Administration approved vandetanib (Caprelsa tablets; AstraZeneca Pharmaceuticals LP) for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced, or metastatic disease. Vandetanib is the first drug approved for this indication, and this article focuses on the basis of approval. Approval was based on the results of a double-blind trial conducted in patients with medullary thyroid carcinoma. Patients were randomized 2:1 to vandetanib, 300 mg/d orally (n = 231), or to placebo (n = 100). The primary objective was demonstration of improvement in progression-free survival (PFS) with vandetanib compared with placebo. Other endpoints included evaluation of overall survival and objective response rate. The PFS analysis showed a marked improvement for patients randomized to vandetanib (hazard ratio = 0.35; 95% confidence interval, 0.24–0.53; P < 0.0001). The objective response rate for the vandetanib arm was 44% compared with 1% for the placebo arm. The most common grade 3 and 4 toxicities (>5%) were diarrhea and/or colitis, hypertension and hypertensive crisis, fatigue, hypocalcemia, rash, and corrected QT interval (QTc) prolongation. This approval was based on a statistically significant and clinically meaningful improvement in PFS. Given the toxicity profile, which includes prolongation of the QT interval and sudden death, only prescribers and pharmacies certified through the vandetanib Risk Evaluation Mitigation Strategy Program are able to prescribe and dispense vandetanib. Treatment-related risks should be taken into account when considering the use of vandetanib in patients with indolent, asymptomatic, or slowly progressing disease. Clin Cancer Res; 18(14); 3722–30. ©2012 AACR.

Background
Medullary thyroid cancer (MTC) is a rare tumor arising from the parafollicular C cells of the thyroid. MTC represents approximately 3% to 5% of all thyroid cancers, and the estimated number of new cases of MTC in 2010 is extrapolated to be 1,300 to 2,200 patients in the United States (1). Seventy-five percent of MTC cases are sporadic, whereas the remaining 25% are hereditary and are part of the autosomal dominant disorder multiple endocrine neoplasia type 2 (MEN2). Mutations in the rearranged during transfection (RET) proto-oncogene are found in more than 90% of patients with MEN2A or MEN2B and in familial MTC, which although inherited, is not associated with other endocrine disorders (2). Somatic mutations in RET are found in 40% to 50% of tumors of patients with sporadic MTC (3). A range of point mutations have been found in RET with mutations in codon 918, found in both hereditary and sporadic MTC, associated with a poorer outcome (4). MTC has no hallmark symptoms, and patients most often initially present with a thyroid nodule or mass. Patients with localized symptoms, such as dysphagia, dyspnea, or hoarseness, are more likely to have persistent disease following surgery. Systemic symptoms, such as bone pain or diarrhea, most often occur in patients with distant metastases (5). The etiology of diarrhea may be related to the secretion of calcitonin (CTN), which is produced by the parafollicular C cells of the thyroid (6). CTN levels are useful in predicting residual disease after surgery, and the doubling time of CTN...
may have prognostic implications (7). High levels of CTN, as seen in patients with disseminated metastases, do not usually cause derangements of calcium metabolism (6). Hypocalcemia, however, may be seen in patients with MTC as a result of postsurgical hypoparathyroidism (8).

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. The overall prognosis of MTC is favorable, with a 10-year overall survival rate for patients with tumors confined to the thyroid gland of approximately 95%. However, for patients with distant metastases present at diagnosis, the 10-year overall survival rate is estimated to be only 40% (9). Surgery is the mainstay of treatment, even with the presence of distant metastases. Other modalities that are used for disease control include radiation therapy, radiofrequency ablation, embolization, and radiolabeled antibodies (5, 10).

Until the approval of vandetanib, no systemic agents were approved for the treatment of unresectable MTC. Historically, chemotherapy has been used for advanced disease; however, the experience has largely been limited to case series or case reports. The best-described agent is doxorubicin, with response rates reported to be in the range of 10% to 25% (11, 12). Other chemotherapy agents with reported activity include 5-fluourouracil, capcitabine, cisplatin, and dacarbazine (12–14). Because of the natural history of the disease and the side-effect profile of these cytotoxic agents, it is recognized that patients with metastatic disease may survive years without systemic treatment and that systemic therapy is usually reserved for patients with rapidly progressive distant metastasis (15, 16).

Several clinical trials have reported the use of kinase inhibitors with in vitro activity against RET and VEGF receptors (VEGFR) in early-phase clinical trials in MTC. These agents include vandetanib, sunitinib, motesanib, and XL184. Phase II studies in patients with MTC have shown response rates of 6.3% for sorafenib (17) and 35% for sunitinib (18). Also, a relatively large phase II study in MTC (91 patients) of motesanib, which inhibits wild-type RET but not mutant RET, showed only a 2% response rate, whereas a small study (17 patients) of XL184 showed a 53% response rate (19, 20). Two single-arm phase II studies have been conducted with vandetanib in patients with hereditary MTC with response rates of 20% and 16%, seen with a 300-mg daily dose and a 100-mg daily dose, respectively. The results of the phase III trial of vandetanib in MTC were published following U.S. Food and Drug Administration (FDA) approval (21–23).

**Chemistry**

Vandetanib is chemically described as N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine and has a molecular weight of 475.36. Vandetanib exhibits pH-dependent solubility, with increased solubility at lower pH.

**Pharmacology and toxicology**

Vandetanib is a multikinase inhibitor of the VEGFR, epidermal growth factor receptor (EGFR), and RET kinase. Additional kinases identified as targets in these experiments include protein tyrosine kinase 6 (BRK), TIE2, and members of the EPH kinase and Src family tyrosine kinase families. The N-desmethyl metabolite of vandetanib was found to have similar inhibitory activity to vandetanib for inhibition of VEGFRs (KDR and Flt-1), EGFR, and basic fibroblast growth factor receptor (24).

In vivo effects of vandetanib were shown using angiogenesis assays and human tumor xenograft models in nude mice. In a study on VEGF165-induced angiogenesis with matrigel plugs in athymic nude mice, treatment with vandetanib decreased the number of vessel nodes and vessel length compared with vehicle. Vandetanib has also been shown to inhibit tumor growth in a variety of human cancer xenografts. A dose of 150 mg/m² of vandetanib inhibited VEGFR2 phosphorylation and phosphorylated EGFR staining in 2 distinct tumor xenograft models. These studies provide some evidence that vandetanib has in vivo activity against VEGFR and EGFR (24).

Vandetanib was not mutagenic in vitro in the bacterial reverse mutation (Ames assay) or clastogenic in the in vitro cytogenic assay using human lymphocytes or in the in vivo rat micronucleus assay. Given the long natural history of MTC and the potential for prolonged vandetanib use, carcinogenicity studies are being done as postmarketing requirements.

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/d. When administered during organogenesis, vandetanib caused malformations of the heart vessels and delayed ossification of the skull, vertebrae, and sternum at all doses tested. The reproductive and developmental toxicology studies suggest that administration of vandetanib may also impair fertility. Vandetanib was assigned pregnancy category D.

In an animal model of wound healing, mice dosed with vandetanib had reduced skin-breaking strength compared with controls. The appropriate interval between discontinuation of vandetanib and subsequent elective surgery, required to avoid the risks of impaired wound healing, has not been determined.

Repeat dose toxicity studies showed damage to the kidneys, spleen, and thymus in both the rat and dog. Additionally, toxicities were observed in the adrenal gland, bile duct, heart, kidneys, lungs, mesenteric lymph nodes, pancreas, skin, and teeth in the rat and gastrointestinal tract in the dog. Nodular masses were observed in multiple organs in the 6-month toxicity study in the rat. Masses were palpable during clinical assessments and were associated with hemorrhagic or inflammatory findings. Dose-dependent prolongation of the corrected QT interval (QTC) and increased blood pressure were observed in dogs after they received a dose of vandetanib that approximates the clinical dose on an mg/m² basis.
**Clinical pharmacology**

A population pharmacokinetic analysis of vandetanib was conducted in 231 patients with MTC following daily oral administration of the 300-mg dose. The pharmacokinetics of vandetanib are characterized by a mean clearance of approximately 13.2 L/h, a mean volume of distribution of approximately 7,450 L, and a median plasma half-life of 19 days.

Absorption of orally administered vandetanib is slow, with peak plasma concentrations achieved at a median of 6 hours, with a range of 4 to 10 hours, after dosing. Vandetanib accumulates approximately 8-fold on multiple dosing with steady state achieved in approximately 3 months. Vandetanib binds to human serum albumin and $\alpha$1-acid-glycoprotein with in vitro protein binding being approximately 90%. In vivo plasma samples from patients with colorectal cancer at steady-state exposure after 300 mg once daily, the mean percentage protein binding was 93.7% (range, 92.2%–95.7%).

Both urine and fecal excretion are the major routes of elimination of vandetanib. In the human Absorption, Distribution, Metabolism, and Excretion (ADME) study, 44% and 25% of the administered radioactive dose (800 mg $^{14}$C-vandetanib) was recovered in feces and urine, respectively.

Vandetanib is a substrate of CYP3A4. Drugs that are CYP3A4 inducers can alter vandetanib plasma concentrations. The concomitant use of known strong CYP3A4 inducers should be avoided while receiving vandetanib therapy. St. John’s wort may decrease vandetanib exposure unpredictably and should be avoided. In healthy subjects, no clinically significant interaction was shown between vandetanib and the potent CYP3A4 inhibitor itraconazole. Vandetanib is a weak inhibitor of CYP2D6 and 2C8. It is not an inducer of CYP enzymes.

No effect of mild hepatic impairment was observed on model-estimated clearance of vandetanib. However, as data are limited in patients with moderate and severe hepatic impairment, vandetanib is not recommended for use in patients with moderate and severe hepatic impairment.

For the moderate and severe renal impairment groups, increases in area under the curve were 39% and 41%, respectively. In these subjects, exposure to the $N$-desmethyl and $N$-oxide metabolites was increased up to 2-fold and 4-fold, respectively. This increased exposure may be a consequence of a shift to an increased metabolic clearance of vandetanib, which compensates for some of the reduced intrinsic clearance due to renal impairment. A dose reduction to 200 mg for patients with moderate and severe renal impairment is recommended.

**Clinical Studies**

**Study design**

Approval of vandetanib was based primarily on the results of a single double-blind, randomized, placebo-controlled phase III trial (study 58) comparing vandetanib, 300 mg daily administered orally ($n = 231$), with placebo ($n = 100$) in patients with unresectable, locally advanced, or metastatic MTC. Patients were treated until investigator-determined progression. Eligibility required measurable disease; however, no criteria specified the pace of disease or the need for treatment. This lack of criteria is an important concern in MTC, in which it is recognized that the natural history of the disease makes observation an acceptable option, even in the setting of metastatic disease.

**Objectives**

The primary objective of this study was to show an improvement in progression-free survival (PFS) with vandetanib compared with placebo in patients with unresectable, locally advanced, or metastatic MTC.

Key secondary endpoints included overall response rate, duration of response, overall survival, CTN and carcinoembryonic antigen (CEA) responses, and time to worsening pain. PFS and response rates were based on centralized, independent review of patient scans.

**Patient baseline characteristics**

The treatment arms were balanced with respect to age, sex, and race. This international trial enrolled 331 patients in 23 countries. Almost all patients were Caucasian, and 22% of patients were enrolled in the United States. Ninety-five percent of patients had stage IVc disease at entry. The majority of patients had a history of prior thyroidectomy and lymphadenectomy. Approximately 80% of patients had a history of radiation therapy, and 20% of patients had prior cytotoxic chemotherapy, such as doxorubicin and/or cisplatin, whereas 10% of the patients had prior targeted therapy.

The median time from diagnosis of MTC to enrollment in the trial was 6 years. The median time from last documented disease progression was approximately 2 months, but 30% of the patients had a progression-free interval of greater than 6 months prior to entering the trial. No information was available on the pace of disease.

**Study 58 efficacy results**

The result of the PFS analysis, based on the independent assessment, showed a statistically significant improvement for patients randomized to vandetanib [hazard ratio (HR) = 0.35; 95% confidence interval (CI), 0.24–0.53; $P < 0.0001$]. The median PFS was not reached for the vandetanib arm, compared with a 16-month median PFS for the placebo arm (Fig. 1). Ninety-six percent of the patients on trial were WHO performance status 0 or 1. Because symptoms of pain or diarrhea may occur, a post hoc analysis of symptomatic patients versus asymptomatic patients was done using the following definition of asymptomatic: patients with a WHO performance status of 0 AND a stool frequency less than 4 times per day AND no pain on average at baseline of any type. The effect of vandetanib on PFS was consistent in both subsets (HR 0.38; 95% CI, 0.2–0.75 for asymptomatic versus HR 0.31; 95% CI, 0.19–0.53 for symptomatic patients). Likewise, the HRs were consistent for all patient subsets, including patients grouped according to last documented progression, time from diagnosis, and baseline metastatic progression, time from diagnosis, and baseline.

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tumor burden, and for prespecified subgroup analyses of gender, WHO performance status, and prior therapy.

At the time of the primary analysis of PFS, 15% of the patients had died, and no significant difference in overall survival was found between the 2 treatment groups. Although this study is not powered for overall survival, a final analysis of this endpoint will occur at 50% of events, which is anticipated to be in 2013. The objective response rate for patients randomized to vandetanib was 44% compared with 1% for patients randomized to placebo. All objective responses were partial responses. The median duration of response for patients treated with vandetanib was not reached.

A key secondary endpoint is the time to worsening pain, which is based on patient opioid use and patient questionnaires. However, a large amount of data were missing, and thus, the results were insufficient to draw any conclusions about this endpoint.

Tumors were assessed for RET mutations; however, 41% of tumors could not be completely assessed for RET mutations, and tumors derived from only 8 patients (2%) could be definitively labeled as RET-mutation negative. Due to the limitations of the RET mutation assay, evidence is insufficient to determine a relationship between the efficacy of vandetanib and RET mutations (25).

The FDA conducted an exploratory analysis of exposure-response relationships in study 58. The trough concentrations at day 56 were divided into quartiles, and a Kaplan–Meier analysis was conducted to assess PFS in patients achieving different concentrations of vandetanib at steady state. The PFS curves of patients in different quartiles were not significantly different from each other, indicating a lack of relationship between steady-state plasma concentrations and PFS over this range. However, it was noted that the quartile with the highest trough concentrations at day 56 showed the worst PFS among the quartiles (Fig. 2; ref. 26).

Safety

Safety data were primarily derived from the phase III trial but were supplemented by adverse event information from other clinical studies using vandetanib. The phase III trial included safety assessments at baseline, weekly for the first 2 weeks, then at 4, 8, and 12 weeks after randomization, and then every 12 weeks thereafter. Safety assessments included medical, oncologic, and surgical history, physical examination, laboratory values (hematology, chemistries, liver function, CTN and CEA, and 24-hour urinalysis), assessment of WHO performance status, 12-lead electrocardiography (ECG), and assessment of concomitant medications. Ophthalmologic examinations were done at screening and at 9 months after patients began receiving treatment. Patients who complained of visual symptoms underwent an ophthalmologic examination at the time the symptom was noted. Only 63.7% of patients underwent an examination during randomized treatment.

Adverse reactions resulting in death in patients receiving vandetanib (n = 5, 2%) were respiratory failure, respiratory arrest, aspiration pneumonia, cardiac failure with arrhythmia, and sepsis. Adverse reactions resulting in death in patients receiving placebo (2%) were gastrointestinal hemorrhage (1%) and gastroenteritis (1%). In addition, 1 sudden death and 1 death from cardiopulmonary arrest occurred in patients receiving vandetanib after data cutoff. Within the vandetanib clinical program, the most common cause of death in patients who received vandetanib was pneumonia.
Treatment discontinuations due to adverse reactions occurred in 12.1% of patients who received vandetanib and 3% of patients on placebo. The most common adverse reactions leading to treatment discontinuation on the vandetanib arm were gastrointestinal disorders (3.0%), which included diarrhea (0.9%), dysphagia (0.4%), nausea (0.4%), pancreatitis (0.4%), peritonitis (0.4%), small intestinal perforation (0.4%), and vomiting (0.4%); asthenia and fatigue (2.6%); skin and subcutaneous disorders (1.7%), including rash (1.3%), eczema (0.4%), photosensitivity reactions (0.4%), and pruritis (0.4%); QTc prolongation (0.9%); elevated creatinine (0.9%); and hypertension (0.9%).

Dose reductions or dose interruption were reported in 49.4% of vandetanib-treated patients and 15.2% of placebo patients. Eighty-one patients (35.1%) on the vandetanib arm were dose reduced to 200 mg, and further dose reduction to 100 mg was required in an additional 32 patients (13.9%). The most common reasons for dose reductions were diarrhea, QTc prolongation, and rash. Dose delays were reported in 47.2% of vandetanib-treated patients and 15.2% of placebo-treated patients.

Serious adverse events occurred in 30.7% of patients on the vandetanib arm and 13.1% of patients on the placebo arm. Serious adverse events in 2% or more of patients in the vandetanib arm included diarrhea, intestinal perforation, pneumonia, and hypertension. Grade 1 to 4 adverse events were seen in 55.4% of patients in the vandetanib arm.

Table 2 provides the frequency and severity of laboratory abnormalities reported for patients with MTC. Alanine aminotransferase (ALT) elevations occurred in 51% of patients on vandetanib. Grade 3 to 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 on a 300-mg dose of vandetanib. Seven patients who continued vandetanib had a normal ALT within 6 months of continued treatment. In the protocol, ALT was monitored every 3 months and more frequently as indicated.

Thyroid-stimulating hormone (TSH) was elevated in 78% of patients receiving vandetanib versus 21% on placebo, and 27% of patients had TSH values greater than 5 times the upper limit of the reference range while on treatment, compared with 3% on placebo. The majority of patients were noted to have increased TSH on their day 28 visit; however, it was noted as early as day 14 and at least as late as day 84. Increases in the dose of the thyroid replacement therapy were required in 49% of the patients randomized to vandetanib, compared with 17% of the patients randomized to placebo. Hypocalcemia was seen in 57% of the patients randomized to vandetanib, compared with 25% on placebo.
QT prolongation
Vandetanib is proarrhythmic. In the phase III clinical trial, vandetanib was associated with sustained plasma concentration-dependent QT prolongation. Based on the exposure-response relationship, the mean (90% CI) QTc change with Fridericia correction (QTcF) 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). The sustained, higher QTc prolongation is likely to be associated with the long half-life of vandetanib (19 days). In addition, about 36% of the patients in the vandetanib arm experienced a greater than 60-ms increase in QTc interval. A higher percentage of patients with changes in QTc greater than 60 ms or with a QTc greater than 480 ms was observed in patients with mild-to-moderate renal function compared with patients with normal renal function. Although no cases of Torsades de pointes (TdP) were found in the randomized trial, 2 cases of TdP were captured in the safety database.

Other toxicities of concern
The majority of the severe adverse events seen with both EGFR and VEGFR inhibitors have been reported with vandetanib, such as rash, including Stevens–Johnson syndrome, ischemic arterial events, interstitial lung disease, intestinal perforations, and reversible posterior leukoencephalopathy syndrome. Although Stevens–Johnson syndrome is uncommon, lethal reactions have occurred. Risk factors for evolution of rash into Stevens–Johnson syndrome are unclear, with 8 of 21 patients receiving radiation prior to development of Stevens–Johnson syndrome.

Cerebrovascular events seem to be increased with vandetanib. During the randomized portion of the phase III study, cerebrovascular events (cerebral ischemia, transient ischemic attack) occurred in 1.3% of patients in the vandetanib group and in no patients in the control arm, whereas coronary occlusion was reported in 1 (0.4%) patient in the vandetanib arm and in no patients in the control arm. This increase in cerebrovascular events seems to be consistent across the randomized trials (26).

Interstitial lung disease and pneumonitis have also been reported more frequently in patients receiving vandetanib than in those randomized to placebo. In a large study of patients with non–small cell lung cancer, interstitial lung disease and pneumonitis were reported in 3.5% of patients receiving 100-mg vandetanib + docetaxel and in 2.0% of placebo (27).

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Vandetanib, 300 mg (n = 231)</th>
<th>Placebo (n = 99)</th>
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<tbody>
<tr>
<td>Diarrhea and/or colitis</td>
<td>132 (57%)</td>
<td>27 (27%)</td>
</tr>
<tr>
<td>Rash</td>
<td>123 (53%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Dermatitis acneform and/or acne</td>
<td>81 (35%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>77 (33%)</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Hypertension/hypertensive crisis/accelerated hypertension</td>
<td>78 (33%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>59 (26%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55 (24%)</td>
<td>23 (23%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>49 (21%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>48 (21%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Dry</td>
<td>35 (15%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34 (15%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Astenia</td>
<td>34 (15%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>ECG QT prolonged</td>
<td>33 (14%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>31 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>30 (13%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>26 (11%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>25 (11%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>25 (11%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Cough</td>
<td>25 (11%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>25 (11%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>24 (10%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>23 (10%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Depression</td>
<td>22 (10%)</td>
<td>3 (3%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes rash, rash erythematous; generalized, macular, maculo-papular, papular, pruritic, and exfoliative rash; dermatitis; dermatitis bullous; generalized erythema; and eczema.

<sup>b</sup>Includes abdominal pain, upper abdominal pain, lower abdominal pain, and abdominal discomfort.

<sup>c</sup>69% had QT prolongation > 450 ms, and 7% had QT prolongation > 500 ms by ECG using Fridericia correction.

Table 1. Adverse reactions in 10% or more of patients on vandetanib during randomized treatment

FDA Approval Summary of Vandetanib in Medullary Thyroid Cancer
those treated with docetaxel alone (26). Overall, 23 patients have been reported to have grade 3 to 4 interstitial lung disease or pneumonitis, with at least 8 patients receiving prior radiation to the chest. Although the overall number of patients is small, the number of patients with dyspnea or hypoxia is much larger. For example, whereas grade 3 to 5 interstitial lung disease and/or pneumonitis was reported in 23 patients, dyspnea and/or hypoxia was reported in 392 (13.0%) patients in the vandetanib safety database and was grade 3 to 4 in 108 (3.6%) patients.

Blurred vision was more common in patients who received vandetanib versus patients who received placebo (9% versus 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 these symptoms will improve after discontinuation.

Discussion

The FDA’s Orphan Drug Designation program provides orphan status to drugs and biologics that are defined as those intended for the safe and effective treatment, diagnosis, or prevention of rare diseases and/or disorders that affect fewer than 200,000 people in the United States. The FDA remains committed to advancing and evaluating new therapies for small populations. The study in MTC shows the ability to conduct well-designed trials even in small populations.

The recommendation for approval was based on the single randomized clinical trial in which vandetanib showed a clinically and statistically significant PFS advantage compared with placebo in patients with locally advanced or metastatic MTC. However, treatment with vandetanib was also associated with frequent and serious side effects. Because of vandetanib’s toxicity profile, treatment should be reserved for patients with symptomatic or progressive disease that is not amenable to surgery or other localized therapy. This approach is consistent with the current management strategy and use of systemic agents in the treatment of patients with MTC.

The mean increase in QTcF with 300 mg of vandetanib is 35 ms. This level of increase is consistent with that seen in antiarrhythmic drugs such as sotalol. Clinical trials infrequently capture TdP, even with drugs known to have significant proarrhythmic effects. In a study conducted in Sweden of patients receiving any proarrythmic drug, the incidence of TdP was estimated at approximately 4 cases per 100,000 (27). In the vandetanib clinical development program, 2 cases in approximately 3,000 patients were found. Few TdP events in a clinical trial do not provide reassurance of safety, and the fact that 2 events were seen in such a limited patient population reveals that there is a significant safety signal.

The proarrhythmic potential of vandetanib is a major concern in the MTC population. Patients with MTC are at higher risk of electrolyte imbalances that may predispose them to a prolonged QT interval, TdP, or sudden death. These imbalances may be a result of prior parathyroidectomy, which can lead to hypocalcemia; chronic diarrhea, often a sequela of increased CTN levels; or treatment with vandetanib, which can lead to both hypocalcemia and chronic diarrhea. In addition, bradycardia, which may arise with increases in TSH level, as was seen with vandetanib.

Table 2. Laboratory abnormalities in patients with MTC

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>All grades</th>
<th>Grade 3–4</th>
<th>All grades</th>
<th>Grade 3–4</th>
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</thead>
<tbody>
<tr>
<td>Chemistries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>132 (57%)</td>
<td>13 (6%)</td>
<td>25 (25%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>118 (51%)</td>
<td>4 (2%)</td>
<td>19 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>55 (24%)</td>
<td>0</td>
<td>7 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>38 (16%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>29 (13%)</td>
<td>0</td>
<td>17 (17%)</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>17 (7%)</td>
<td>1 (&lt;1%)</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Calcium increased</td>
<td>16 (7%)</td>
<td>2 (1%)</td>
<td>9 (9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>15 (6%)</td>
<td>1 (&lt;1%)</td>
<td>3 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>13 (6%)</td>
<td>1 (&lt;1%)</td>
<td>4 (4%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>12 (5%)</td>
<td>4 (2%)</td>
<td>7 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium increased</td>
<td>6 (3%)</td>
<td>0</td>
<td>4 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC decreased</td>
<td>45 (19%)</td>
<td>0</td>
<td>25 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>31 (13%)</td>
<td>1 (&lt;1%)</td>
<td>19 (19%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>21 (10%)</td>
<td>1 (&lt;1%)</td>
<td>5 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>18 (9%)</td>
<td>0</td>
<td>3 (3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: WBC, white blood count.
treatment, may place the patient with MTC at risk for serious cardiac arrhythmias and events. Management of QT prolongation may be complicated by the 19-day half-life of vandetanib.

Because of the risk of QT prolongation, TdP, sudden death, and the natural history of the disease, vandetanib was approved with a Risk Evaluation and Mitigation Strategy (REMS) to include Elements to Assure Safe Use. Only prescribers and pharmacies certified with the vandetanib REMS Program will be able to prescribe and dispense vandetanib. The goal of the REMS is to reduce the incidence of TdP and sudden death by educating prescribers and patients about the risks of QT prolongation, the appropriate monitoring of the QT interval and of electrolytes, and the management of QT prolongation, given the long half-life of vandetanib. In addition, the applicant has been required to conduct postmarketing studies evaluating a lower dosage of vandetanib, ejection fraction, and eye abnormalities.

The relationship between drug concentration efficacy and toxicity remains to be explored. For unclear reasons, the highest steady-state concentrations at day 56 showed the worst PFS among the various quartiles examined. On the other hand, patients who had their doses reduced to 200 mg or 100 mg by day 84 showed comparable PFS to those other hand, patients who had their doses reduced to 200 mg of vandetanib, suggesting that lower doses may also provide effective therapy. Given the small number of patients in each quartile, it is impossible to make any sweeping conclusions about what these findings suggest; however, the concern about the use of a lower dose in this patient population will be addressed in a separate postmarketing trial.

The FDA’s approval of vandetanib is the first approval for systemic therapy in MTC and is the first molecularly targeted agent approved for this disease. This therapy provides a new treatment option for patients with symptomatic, progressive advanced MTC.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

The opinions expressed in this article do not necessarily reflect those of the FDA or the U.S. Government. There are no restrictions on its use with the exception of any previously printed figures and tables.

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