CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203756Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA #	NDA 203756
Applicant Name	Exelixis Inc.
Date of Submission	May 21, 2012 (receipt date May 29, 2012)
PDUFA Goal Date	November 29, 2012
Proprietary Name / Established (USAN) Name	COMETRIQ cabozantinib
Dosage Forms / Strength	COMETRIQ 20-mg gelatin capsules; grey capsules with "XL184 20mg" printed in black on the capsule COMETRIQ 80-mg gelatin capsules: Swedish orange with "XL184 80mg" printed in black on the capsule
Proposed Indication(s)	COMETRIQ is indicated for the treatment of patients with progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC)
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Patricia Keegan
Regulatory Project Manager Review	Gina Davis
Medical Officer Review	Ruthann Giusti
Statistical Review	Yuan-Li Shen
Pharmacology Toxicology Review	Margaret Brower
CMC Review	Minerva Hughes, William M. Adams, Li-Shan Hsieh
Microbiology Review	Denise Miller
Clinical Pharmacology Review	Jun Yang
OPDP	Carole Broadnax & Karen Munoz-Nero
OMP/DMPP Review	Karen Dowdy
DMHS Review	Jeanine Best
OSI	Roy Blay
CDTL Review	Suzanne Demko
OSE/DMEPA	James Schlick
OSE/DRISK	Joyce Weaver
QT/IRT Consult	Satjit Brar

OND=Office of New Drugs
OMP=Office Medical Policy
DMPP=Division of Medical Policy Program
OPDP= Office of Prescription Drug Promotion
PMHS= Pediatric and Maternal Health Staff
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

Cabozantinib is an inhibitor of multiple tyrosine kinases, including RET, MET, and VEGFR2. Cabozantinib in medullary thyroid cancer (MTC) is a targeted therapy, based on the known correlation between mutation in the *RET* gene and both the hereditary and sporadic forms of MTC. Cabozantinib has the same mechanism of action (inhibition of RET tyrosine kinase) as vandetanib, which was approved for the treatment of metastatic MTC in 2011, based on a similarly designed trial and endpoints (progression-free survival and durable objective response rate) as cabozantinib.

This NDA is supported by a single, well-conducted, placebo-controlled, randomized (2:1), multi-national trial (Protocol XL184-301), which enrolled 330 patients with metastatic MTC. Assessment for *RET* mutation was not a requirement of the protocol but was assessed retrospectively in approximately 70% of patients with "research-use only" assays. Protocol XL184-301 demonstrated that treatment with cabozantinib results in a statistically significant and clinically important improvement in progression free survival [HR 0.28 (95% CI: 0.19, 0.40); p<0.0001], with an estimated median PFS of 11.2 months for cabozantinib compared to 4 months for patients receiving no treatment (placebo arm). The favorable results from the cabozantinib arm were robust based on various sensitivity analyses and consistent within relevant patient subgroups, including subgroups retrospectively identified as *RET* mutation positive, *RET* mutation negative, and *RET* mutation status unknown. In addition, there was a significantly higher overall response rate (27%) for cabozantinib-treated patients as compared to no responses in the placebo arm.

In a planned interim analysis (conducted after 44% of the total deaths for the final analysis of survival), and in an unplanned analysis (conducted at FDA's request with 75% of the planned deaths for the final analysis), there was no evidence of significant improvement in overall survival (OS) for cabozantinib-treated patients. The estimated median survival times were 26 months for cabozantinib-treated patients and 20.3 months for placebo-treated patients.

The safety database of 289 patients included the results of the major efficacy trial and two additional, single-arm trials in patients with various cancers, treated with cabozantinib 140 mg daily. In the major efficacy trial, dose modifications occurred in the majority (86%) of patients; the most common adverse reactions resulting in dose modification were palmar-plantar erythrodysesthia syndrome, weight loss, decreased appetite, fatigue, diarrhea, stomatitis, asthenia and nausea.

There was no difference in OS between the two treatment arms, although four deaths in the cabozantinib arm were considered probably related to treatment (1 death due to fatal hemorrhage, 2 deaths in patients with esophageal fistula formation, and 1 death due to respiratory failure in a patient with hemorrhage and possible fistula). The most common serious adverse reactions of cabozantinib are gastrointestinal (GI) perforations, GI and non-GI fistulas, thrombotic events, hemorrhage, wound complications, hypertension, osteonecrosis, and reversible posterior leukoencephalopathy syndrome. The most common (≥ 30%) adverse reactions of cabozantinib are diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, weight loss, decreased appetite, nausea, fatigue, oral pain, dysgeusia, oral pain, depigmentation of hair, and hypertension.

The major issue considered during this review was the acceptability of the proposed dose in light of the adverse reaction profile and given the lack of a clear exposure-response relationship in exploratory analyses conducted by the Clinical Pharmacology reviewers. Based on this concern, a post-marketing trial will be required to explore the safety and activity of a lower dose of cabozantinib.

2. Background

Indicated population/available therapy

Medullary thyroid cancer arises from the parafollicular cells of the thyroid and is reported to account for 3-5% of estimated 56, 460 cases of cancers of the thyroid gland estimated to occur in 2012. [1,2] Approximately one-quarter of MTC are hereditary and mutations of the *RET* (REarranged during Transfection) gene occur in 95% of these hereditary MTC cases, while the proportion of sporadic MTC with RET mutations is reportedly lower (25%)[3]. Mutation of *RET* leads to activation of receptor tyrosine kinases, with downstream activation of pathways involved in cell proliferation. Cabozantinib is designed to target this pathway common to hereditary MTC and some cases of sporadic MTC.

On April 6, 2011 Caprelsa (vandetanib), an inhibitor of the RET, VEGFR2, and other kinases, was approved for "the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib." Vandetanib was approved under a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU) based on the risks of Torsades de pointes and sudden death due QT prolongation. In addition, vandetanib labeling contains Warnings and Precautions describing the following additional clinically important adverse reactions: skin reactions and Stevens-Johnson Syndrome, interstitial lung disease, ischemic cerebrovascular events, hemorrhage, heart failure, diarrhea, hypothyroidism, hypertension, Reversible Posterior Leukoencephalopathy Syndrome, drug interactions, renal impairment, hepatic impairment, and Pregnancy Category D.

3. CMC

There are no outstanding CMC issues that preclude approval. Chemistry reviewers have provided an overall acceptability of the manufacturing of the drug product and drug substance. There were no microbiology deficiencies noted in the NDA submission. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months at ambient room temperature. All quality and compliance reviewers recommended approval.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding pharmacology/toxicology issues that preclude approval.

This NDA contained nonclinical studies assessing the pharmacology, safety pharmacology, chronic toxicology, and reproductive toxicology of cabozantinib. The pharmacology of cabozantinib itself was similar to that in humans; however, the concentration of active metabolites of cabozantinib were substantially lower in animals than in humans requiring that a post-marketing study be required for to assess the potential genotoxicity of the M4 metabolite.

Studies in rats and dogs suggest that fertility may be impaired in cabozantinib-treated males and females. In safety pharmacology trials, cabozantinib did not inhibit hERG channel activity at relevant concentrations and no effects on cardiovascular parameters were observed in dogs. In safety pharmacology studies conducted in rats, behavioral and physiological changes were not observed following single doses of up to 300 mg/kg cabozantinib and single doses of 900 mg/kg cabozantinib had no effects on respiratory parameters.

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[1] http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional/page7
[2] Pitt SC, Moley JF: Medullary, Anaplastic, and Metastatic Cancers of the Thyroid. Semin Oncol 37 (6): 567-579, 2010.
[3] Liu Z, Falola J, Zhu X, et al: Antiproliferative effects of Src inhibition on medullary thyroid cancer. J Clin Endocrinol Metab 89:3503-3509, 2004.

Cabozantinib was not mutagenic or clastogenic. Genotoxic impurities were considered adequately characterized. The four major metabolites of cabozantinib were not mutagenic but have not been assessed for induction of chromosomal aberrations. However, based on the potential for long-term survival in some patients with medullary MTC (median survival from diagnosis is X), the nonclinical review team has identified the requirement for 2-year carcinogenicity studies in rats and mice.

Embryofetal development studies were conducted in rats and rabbits. In both species, there was increased risk of post-implantation losses at cabozantinib exposures of < 1% (rats) and 9-11% (rabbits) of the human exposure at the recommended dose of 140 mg compared to controls. Additional findings includes cardiac anomalies, and dose-dependent increases in skeletal variations in rats and a dose-dependent decrease in fetal body weight, increases in the incidence of visceral variations and malformations including reduced spleen size and missing lung lobes in rabbits at exposures significantly lower than the human exposure at the recommended dose. Reproductive toxicity findings suggest that male and female fertility can be impaired by treatment with cabozantinib. Based on these findings, product labeling identifies this product as Pregnancy Category D. In addition, based on the potential for extended survival in some patients with medullary thyroid cancer, and the known pharmacologic effects of inhibition of MET and VEGF pathways which may result in altered bone development, a post-marketing requirement for a pre/post-natal developmental toxicity study has been identified.

5. Clinical Pharmacology

There are no outstanding clinical pharmacology issues that preclude approval.

The pharmacokinetics of cabozantinib capsules and cabozantinib "powder in bottle" dosage forms were evaluated in healthy subjects and in patients with cancer. Results from a population PK analysis demonstrate that the half-life of cabozantinib at steady state was approximately 55 hours, the oral volume of distribution is approximately 349 L, and clearance (CL/F) was estimated to be 4.4 L/hr. The median Tmax was approximately 2-4 hours in cancer patients following a single oral dose. Mass balance studies in healthy subjects demonstrated that 54% of administered radioactivity was recovered in the feces and 27% was recovered in the urine. The dose proportionality of the cabozantinib capsules has not been evaluated, however dose-proportional AUC and Cmax were observed with the "powder in bottle" dosage form. Absolute oral bioavailability of cabozantinib capsule has not been determined. Significant increases in Cmax (41%) and AUC (57%) were observed when cabozantinib was administered with a high-fat, high calorie meal in healthy subjects, thus product labeling states that cabozantinib should be taken without food.

The Clinical Pharmacology review team recommended that the dosing regimen in product labeling be based on PK modeling, with a proposed starting dose of 100 mg daily, to be increased to 140 mg or decreased to 60 mg based on observed toxicity. This recommendation was based on the observation that 86.4% of the patients in the major efficacy trial required dose modification (interruption, reduction, or termination), on exposure-response analyses suggesting that progression-free survival was similar across all quartiles for cabozantinib exposure, and a correlation observed between model-predicted steady state exposure ($AUC_{SS\ PRED}$) and time to first dose medication (shorter time with higher exposure). It is noted that there was no correlation between exposure and the incidence of the most common adverse reactions resulting in dose modification (palmar-plantar erythrodysesthesia or diarrhea). Dr. Jun concluded that "These E-R relationships for efficacy and safety suggest that a lower dose might be effective with improved tolerability; therefore, label should include a starting dose of 100 mg with a provision to increase the dose to 140 mg or decreased to 60 mg as tolerated."

Given the exploratory nature of the exposure-response analysis performed using the results for sparse PK sampling techniques in 200 patients per Table 5 of Dr. Jun's review, it is Dr. Keegan's opinion that the data are inadequate to support a recommended dose that has not been studied. As an alternative, the clinical and clinical pharmacology review teams have agreed that a postmarketing trial is required to confirm that an alternative dosing regimen is safer and retains sufficient efficacy.

The results of the population PK analyses do not identify clinically relevant differences in exposures based on gender, age, or race (White versus non-White) and that the effect of mild and moderate renal impairment on clearance of cabozantinib is minimal. Since cabozantinib is cleared by the kidneys and metabolized, via CYP3A4, in the liver and formal studies of the PK of cabozantinib in patients with renal or hepatic organ impairment have not been conducted, PK studies in patients with severe renal impairment and hepatic impairment are required. Pending the completion of the hepatic impairment trial, product labeling contains a Warning that cabozantinib is not indicated for the treatment of patients with hepatic impairment. In addition, product labeling contains recommendations to avoid use of strong CYP3A4 inducers or inhibitors in patients receiving cabozantinib, and proposes specific recommendations for dose modification based on the dedicated drug interactions studies of cabozantinib in patients taking strong CYP3A4 inducers or inducers. Dedicated studies have shown that cabozantinib exposure is increased by 38% when administered to subjects taking a strong CYP3A4 inhibitor and that cabozantinib exposure is decreased by 77% in subjects taking a strong CYP3A4 inducer.

Population PK studies were inconclusive regarding the effects of gastric pH modifying agents on cabozantinib PK. Since the solubility of cabozantinib is pH-dependent, the clinical pharmacology review team has stated that a post-marketing trial to conduct a dedicated study assessing the effects on pH modifying agents on cabozantinib pharmacokinetics also be required.

The effects of cabozantinib on the QT interval were assessed in a dedicated substudy within the major efficacy trial. The IRQT consultant's assessment of this substudy was that no large increases in mean QT interval (>20 ms) were detected at steady state (pre-dose on Cycle 2, Day 1) compared to baseline values in the 166 cabozantinib-treated patients assessed on C2D1. The mean change was 11.3 ms (90% CI: 8.7, 13.95). There were no new changes in cardiac wave form morphology or new rhythms in patients with increased QT interval and no cabozantinib -treated patient had a QTcF >500 ms. These results have been described in the Clinical Pharmacology section of product labeling, however based on these data, no Warnings or Precautions are required.

6. Clinical Microbiology

There are no outstanding sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

This NDA was primarily supported by a single international, multi-center, randomized (2:1), placebo-controlled trial enrolling 330 patients with metastatic MTC. Patients were required to have progressive disease within 14 months prior to entry. Patients were randomized to receive cabozantinib 140 mg (n = 219) or placebo (n = 111) orally once daily. Randomization was stratified by age and prior tyrosine kinase inhibitor (TKI) use. Patients were treated until disease progression or intolerable toxicity. At the time of disease progression, cross-over to cabozantinib was not permitted in patients receiving placebo. An independent radiology review committee (IRC), using the modified RECIST criteria, determined radiographic progression and tumor response.

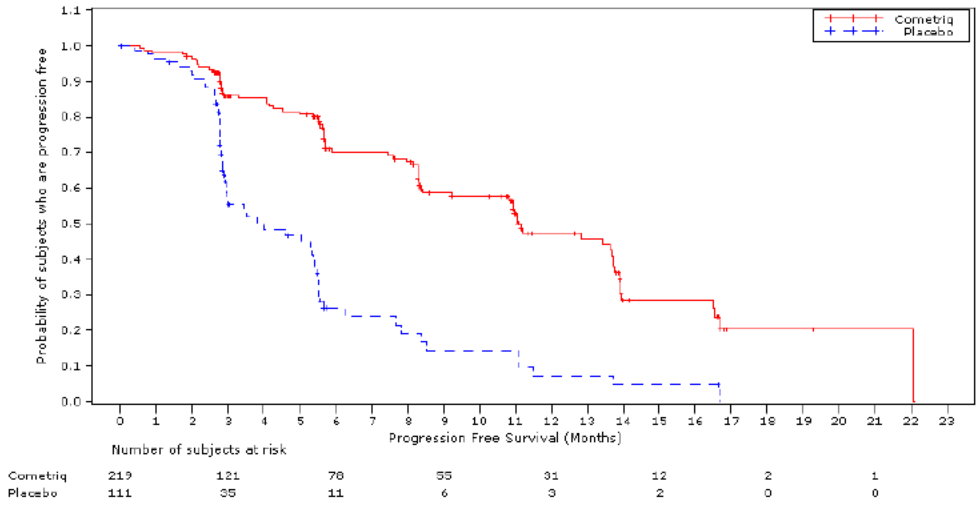
Of 330 patients, 67% were male, the median age was 55 years, 23% were 65 years or older, 54% had a baseline ECOG performance status of 0, and 92% had undergone thyroidectomy. Twenty-five percent (25%) received two or more prior systemic therapies and 21% had been previously treated with a TKI.

A statistically significant PFS prolongation was demonstrated in the cabozantinib arm compared to the placebo arm [HR 0.28 (95% CI: 0.19, 0.40); p <0.0001]. The estimated median PFS was 11.2 and 4.0 months for the cabozantinib and placebo arms, respectively.

The ORR was significantly higher in the cabozantinib arm (27% versus 0%; p<0.0001) and all were partial responses. The median response duration was 14.7 months (95% CI: 11.1, 19.3). No statistically significant difference in overall survival

was observed between the treatment arms at the planned interim analysis and in an updated survival analysis requested by FDA.

The efficacy results, as presented in the statistical review, are abstracted and presented below.



Primary and Secondary Efficacy Endpoints In Protocol XL184-301		
	Cabozantinib (n=219)	Placebo (n=111)
Final analysis - progression-free survival		
Number of PFS events	79	60
Median	11.2 mos	4.0 mos
Hazard Ratio	0.28	
95% CI[1]	(0.19, 0.40)	
p-value[2]	<0.0001	
Interim analysis - overall survival		
Number of OS events	66	30
Median	21.1 mos	NR[3]
Hazard Ratio	0.98	
95% CI	(0.64, 1.54)	
p-value[2]	0.99	
FDA-requested update - overall survival		
Number of OS events	103	59
Median	26.0	20.3
Hazard Ratio	0.825	
95% CI	(0.60, 1.14)	
p-value[2]	0.24	
Final analysis – overall response rate		
Number of Partial Responses[4]	58	0
Overall Response Rate	27%	0
95% CI	(20.8, 32.9)	NA[5]
p-value[6]	<0.0001	
Median duration of response	14.7 mos	NA

[1] confidence intervals [2] stratified log-rank test [3] not reached [4] All responses were partial responses [5] not applicable [6] stratified Cochran-Mantel-Haenszel test

The treatment effect on PFS was consistent across both demographic subgroups (age, gender) and prognostic subgroups (ECOG PS 0 vs. 1 vs. 2), prior lines of therapy (0 vs. 1 vs. ≥2), prior treatment with TKI (yes vs. no) and by RET mutation status. In patients retrospectively identified to have a RET mutation, the hazard ratio was 0.23 (95% CI 0.14, 0.38), while in those identified as RET mutation negative, the hazard ratio was 0.44 (95% CI 0.15, 1.30) and in those without assessment of RET mutation status, the hazard ratio was 0.30 (95% CI 0.16, 0.56). Due to the retrospective nature of the RET mutation testing, convenience sample (31% missing data), and lack of validation of the assay, these results should be viewed cautiously but do suggest that the presence of RET mutation may not be required to achieve a treatment effect. Treatment effects were observed both in patients with hereditary MTC [HR 0.09 (95% CI 0.01, 0.82)] and in those with sporadic MTC [HR 0.32 (95% CI 0.22, 0.46)].

8. Safety

The size of the safety database, which was primarily limited to the major efficacy trial and two additional trials that evaluated the safety of cabozantinib monotherapy in 295 cabozantinib-treated patients, is small but adequate to identify serious adverse reactions. Comparative safety data are available only from the major efficacy trial, with comparison of adverse events in 214 cabozantinib-treated patients with those observed in 109 placebo-treated patients.

There was no difference in overall survival between the two treatment arms; the number of adverse reactions resulting in death during treatment or within 30 days of the last dose of study drug was comparable. Four deaths in the cabozantinib arm were considered probably related to treatment (1 death due to fatal hemorrhage, 2 deaths in patients with esophageal fistula formation, and 1 death due to respiratory failure in a patient with hemorrhage and possible fistula), while the rate of deaths due to sepsis or aspiration pneumonia were similar between the treatment arms.

Selected adverse reactions observed in ≥ 25% of cabozantinib-treated patients and at a higher incidence than in patients receiving placebo (difference ≥ 5%), were diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome (PPES), decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes (hypopigmentation/graying), dysgeusia, hypertension, abdominal pain, and constipation. The most common laboratory abnormalities (≥25%) were increased AST, increased ALT, lymphopenia, increased alkaline phosphatase, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia. Grade 3-4 adverse reactions which occurred in ≥ 5% of cabozantinib-treated patients and at a higher incidence than in patients receiving placebo (difference ≥ 2%), were diarrhea, PPES, lymphopenia, hypocalcemia, fatigue, hypertension, asthenia, increased ALT, decreased weight, stomatitis, and decreased appetite. The following serious adverse reactions attributed to cabozantinib included osteonecrosis of the jaw (n=1), reversible posterior leukoencephalopathy syndrome (n=1), pancreatitis (n=3), nephrotic syndrome (n=1), fatal hemorrhage (n=2), and fatal perforation/fistula (n=2).

9. Advisory Committee Meeting

The NDA was not presented to the Oncologic Drugs Advisory Committee for all of the following reasons: the clinical study design was acceptable; the application did not raise significant safety or efficacy issues that were unexpected for a drug indicated for the treatment of metastatic MTC; and there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

Orphan drug designation, therefore, PREA is not applicable.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: Cometriq (cabozantinib) capsules is acceptable.
- Physician labeling: There are no unresolved issues. There will be a Boxed Warning for treatment-related adverse reactions of Hemorrhage and Perforation/Fistula Formation, which resulted in significant morbidity and treatment-related mortality.
- Carton and immediate container labels: All proposed revisions by ONDQA and DMEPA have been incorporated into carton & container labeling.
- Patient labeling: There are no unresolved issues.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.

- Risk Benefit Assessment
  Medullary thyroid cancer (MTC) is an indolent cancer, with approximately 3000 new cases expected in 2012. Prior to the approval of vandetanib in 2011, there were no FDA-approved agents for metastatic MTC and off-label use of antineoplastic agents yielded limited activity, thus there was a clear unmet need for new treatments.

  Results from the trial that primarily support this NDA show that cabozantinib demonstrated an improvement in median PFS of 7 months, and treatment results in durable tumor responses (27% ORR with median duration of response of 14.7 months). The magnitude of these effects is clinically important and statistically robust. The risks of cabozantinib are well-understood risks common to many antineoplastic agents and considered generally acceptable. The most common serious adverse reactions of cabozantinib are gastrointestinal (GI) perforations, GI and non-GI fistulas, thrombotic events, hemorrhage, wound complications, hypertension, osteonecrosis, and reversible posterior leukoencephalopathy syndrome. The most common (≥ 30%) adverse reactions of cabozantinib are diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, weight loss, decreased appetite, nausea, fatigue, oral pain, dysguesia, oral pain, depigmentation of hair, and hypertension.

  The Risk benefit profile, which was also discussed by Dr. Keegan, Ms. Demko and Dr. Giusti is acceptable. In addition, the review team recommends approval of this NDA, and I concur.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  A REMS is not required to ensure safe use.

- Recommendation for other Postmarketing Requirements and Commitments
  See action letter.

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/s/

TAMY E KIM
11/29/2012

RICHARD PAZDUR
11/29/2012