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RESEARCH**

APPLICATION NUMBER:

202570Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	202570
Supplement #	
Applicant Name	Pfizer Inc
Date of Submission	3/30/11
PDUFA Goal Date	9/30/11
Proprietary Name / Established (USAN) Name	XALKORI/ crizotinib
Dosage Forms / Strength	Capsules, 200 mg and 250 mg
Proposed Indication(s)	Treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)
Action/Recommended Action for NME:	<i>Accelerated Approval</i>

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Shakuntala Malik
Statistical Review	Lijun Zhang, Shenghui Tang, Meiyu Shen
Pharmacology Toxicology Review	Brenda Gehrke, Whitney Helms, John Leighton
CMC Review/OBP Review	Zedong Dong, Debasis Gosh, Donghao Lu, Richard Lostritto, Karen Riviere
Microbiology Review	Stephen Langille
Clinical Pharmacology Review	Pengfei Song, Anshu Marathe
DDMAC	Marybeth Toscano, Richard Lyght
OSI	Robert Young
CDTL Review	Ellen Maher
OSE/DMEPA	Kimberly DeFronzo, Denise Baugh, Kevin Wright
OSE/DDRE	
OSE/DRISK	Latonia Ford, Amarilys Vega
Other: Consults	Wiley Chambers, John Senior

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
 OSI = Office of Scientific Investigations
 DDRE = Division of Drug Risk Evaluation
 DRISK = Division of Risk Management
 CDTL = Cross-Discipline Team Leader

1. Introduction

This new drug application for XALKORI (crizotinib) Capsules was submitted on 3/30/11 for the indication of treatment of patients with anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small cell lung cancer (NSCLC). Because of the high objective response rates in two single-arm trials in patients with ALK-positive NSCLC, the application was given a priority review. This review will briefly discuss the clinical trial efficacy and safety results and the recommendations of each review discipline.

2. Background

Crizotinib is a receptor tyrosine kinase inhibitor with activity against c-MET, RON, ROS, and the active kinase formed by ALK gene rearrangement.

ALK inhibition by crizotinib results in reduced downstream signaling in ERK, Akt, STAT3, and PLC γ 1, pathways known to contribute to cellular growth and development. In animal models, expression of the ALK fusion protein in lung alveolar cells, without other genetic alterations, leads directly to the development of lung cancer. ALK rearrangements are estimated to occur in 1-7% of patients with NSCLC (Clin Cancer Res 2009 15:5216). In October 2007, the sponsor's phase 1 trial was amended to include a phase 2 ALK-positive cohort based on partial responses in 7/14 previously treated patients with ALK-positive NSCLC.

An End-of-Phase 2 meeting was held on 4/23/09. The sponsor asked about accelerated approval based on a single-arm study. The FDA expressed concern about the size of the database and recommended a randomized trial vs. conventional therapy (docetaxel or pemetrexed). Accelerated approval could be considered based on an interim analysis of a surrogate endpoint in the randomized trial. The sponsor was advised to discuss their proposed companion diagnostic with CDRH.

At a meeting on 4/14/10, the sponsor asked whether it would be acceptable to submit an NDA for accelerated approval based on two single-arm trials in patients with ALK-positive NSCLC, if the safety profile remained acceptable and the observed ORR results were maintained. The FDA stated that it would be acceptable to submit the data but whether the response rate would support accelerated approval would be a review issue and would depend on the final response rate, the durations of response, and the risk:benefit ratio. The sponsor also asked whether one phase 3 study (A8081014) would be sufficient for full approval. The FDA cautioned about relying on a single trial, recommended overall survival as the primary endpoint, and stated that whether PFS would support full approval would be a review issue and would likely require an ODAC discussion. There was additional discussion about the companion diagnostic.

A general pre-NDA meeting was held on 7/29/10 to discuss technical aspects of the submission. A CMC pre-NDA meeting was held on 9/24/10.

3. CMC/Device

The CMC review team recommends that this application be approved with the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of fifteen months.

The companion diagnostic, the Vysis ALK Break-Apart FISH Probe Kit (Abbott Molecular, Inc.), will be approved concurrently with crizotinib. The test is designed to detect rearrangements of the anaplastic lymphoma kinase (ALK) gene in NSCLC.

There are no outstanding CMC or device issues.

4. Nonclinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues that preclude the approval of crizotinib in this indication.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology and Biopharmaceutics team recommended approval, and there are no issues that would preclude approval. However, they are recommending several PMRs and PMCs mainly to study drug interactions and dose adjustments with crizotinib based on these interactions. See action letter for these PMRs and PMCs.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This accelerated approval is based on the results of two single-arm studies, Study A (N = 136 patients) and Study B (N = 119 patients). Crizotinib, 250 mg, was administered orally twice daily to a total of 255 patients with locally advanced or metastatic ALK-positive NSCLC. Demographic analysis from the combined data of these trials noted that the median age was 52 years, 63% of patients were Caucasian, 30% were Asian, 48% were male and 84% had an ECOG performance status of 0 or 1. Fewer than 3% of patients were current smokers. Ninety-six percent had adenocarcinoma, 95% had metastatic disease, and 94% had received prior systemic treatment for NSCLC.

The primary endpoint of both trials was objective response rate (ORR) as assessed by the investigator. In Study A, the ORR was 50% (95% CI: 42, 59) with a median response duration of 42 weeks. In Study B, the ORR was 61% (95% CI: 52, 70) with a median response duration of 48 weeks. Complete responses were observed in 1% of patients. No differences in ORR by performance status, the number of prior chemotherapeutic regimens, or the percentage of cells found to have the ALK gene rearrangement were noted. Efficacy data from Studies A and B are provided in Table 1.

Table 1: Locally Advanced or Metastatic ALK-Positive NSCLC Efficacy Results from Studies A and B^a

Efficacy Parameter	Study A N=136	Study B N=119
ORR (CR+PR) ^b [% (95% CI)]	50% (42%, 59%)	61% (52%, 70%)
Number of Responders	68	71
Duration of Response ^c [Median (range) weeks]	41.9 (6.1+, 42.1+)	48.1 (4.1+, 76.6+)

^aResponse as assessed by the Investigator.

^bOne patient was not evaluable for response in Study A; 3 patients were not evaluable for response in Study B.

^cPreliminary estimate using Kaplan-Meier method.

+Censored values

Although this approval will not include the ALK negative NSCLC population, based on Dr. Maher's CDTL review, "23 patients with locally advanced or metastatic ALK negative NSCLC have received crizotinib. Eight of the 23 (34.8%) had not received prior chemotherapy for metastatic disease. Five of 19 patients responded for an investigator response rate of 26.3% (95% CI 9.1%, 51.2%). Two additional patients have a single assessment of PR. If confirmed, the response rate would be 7/20 (35.0%). This is similar to the response rate in patients with ALK positive NSCLC in Study A. It is unclear if this finding is related to the assay or to the ability of crizotinib to

target other genetic abnormalities associated with NSCLC such as c-Met or ROS. The applicant is retrospectively testing tumor samples for the presence of these genetic abnormalities. The study of additional patients with ALK negative NSCLC will be a post-marketing requirement”.

8. Safety

The most common adverse reactions ($\geq 25\%$) observed in both studies were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. Vision disorders included visual impairment, photopsia, vision blurred, vitreous floaters, photophobia, and diplopia. Grade 3-4 adverse reactions in at least 4% of patients included increased ALT and neutropenia. Crizotinib has been associated with severe, life-threatening, or fatal treatment-related pneumonitis with a frequency of 1.6% in clinical trials. All cases occurred within 2 months after the treatment initiation.

9. Advisory Committee Meeting

The application was not referred to an FDA advisory committee because it did not raise significant safety or efficacy issues in the intended population. However, the application was discussed independently with two SGE's. Both recommended approval.

10. Pediatrics

PREA does not apply because of orphan drug exclusivity.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: XALKORI was found to be acceptable by DMEPA.
- Physician labeling: Agreement has been reached on the physician labeling.
- Immediate container labels: Minor problems in the immediate container label were identified by DMEPA and CMC; however, these issues were communicated to the sponsor and resolved.
- Patient labeling: Agreement has been reached on patient labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Accelerated Approval
- Risk Benefit Assessment

Compared to conventional chemotherapy, there was a marked elevation in response rate and duration of response observed in two single-arm studies with crizotinib. It is thought that this will translate into an

improvement in overall survival in this patient population; however, as a condition of accelerated approval, two Phase 3, randomized (crizotinib vs. conventional chemotherapy) confirmatory trials are required to be conducted by the applicant to verify clinical benefit.

Although crizotinib appears to be less toxic than conventional chemotherapy, further follow up and examination of the adverse event profile of crizotinib in a randomized trial will be necessary to fully define the safety signals associated with crizotinib.

The benefits and risks of crizotinib were discussed in the Division Director's Summary Review, the CDTL and Clinical Reviews. The review team found the risk-benefit assessment to be acceptable. In conclusion, I concur with the review team's recommendation for approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

See action letter for PMRs and PMCs. This NDA is being approved under Accelerated Approval, therefore, the sponsor is required to conduct confirmatory trials to be considered for full approval.

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/s/

TAMY E KIM
08/26/2011

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08/26/2011