CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202324Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

Date	January 27, 2012
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	202324
Applicant Name	Pfizer Pharmaceuticals, Inc.
Date of Submission	April 14, 2011
PDUFA Goal Date	February 14, 2012
Proprietary Name / **Established (USAN) Name**	Inlyta axitinib
Dosage Forms / Strength	Tablet/5 mg
Proposed Indication(s)	For the treatment of patients with advanced renal cell carcinoma
Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Deputy Director Summary Review	Amna Ibrahim
Medical Officer Review	Amy McKee/John Johnson
Statistical Review	Somesh Chattopadhyay/ Shenghui Tang/ Raji Sridhara
Pharmacology Toxicology Review	Anwar Goheer/Todd Palmby/John Leighton
CMC Review/ OBP Review	Amit Mitra and Jean Tang/Sarah Pope Miksinski; Kareen Riviere/Angelica Dorantes
Microbiology Review	Denise Miller/Stephen Langille
Clinical Pharmacology Review	Sarah Schrieber/Qi Liu
Pharmacometric Review	Nitin Mehrotra/ Christine Garnett
DDMAC	Marybeth Toscano and Richard Lyght
DSI	Robert Young/ Tejashri S Purohit-Sheth
CDTL Review	John Johnson
OMP	Latonia Ford and Barbara Fuller
OPDP	Michelle Safarik
OSE/DRISK	Joyce Weaver/ Claudia Karwoski

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

1. Introduction

Renal cancer is one of the more common cancers in the US. According to the Seer database, about 61,000 men and women will be diagnosed with and 13,000 will have died from cancer of the kidney and renal pelvis in 2011. Prior to 2005, IL-2 and INF-α were used to treat advanced, inoperable renal cell cancer based on an improvement in response rates, which with IL-2 can be occasionally durable. Both these drugs have substantial toxicity.

Since 2005, 6 agents have been approved for this disease. These include sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab and pazopanib. All of these were approved based on an improvement in progression-free survival (PFS).The only exception is temsirolimus, which has demonstrated an improvement in overall survival (OS) in patients with pre-specified poor prognosis risk factors.

NDA 202324 was submitted for the following proposed indication: *"INLYTA is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma"*

2. CMC/Device

The Chemistry review team recommends an overall acceptability regarding the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months for the drug product when stored at 20-25°C (68-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). There are no outstanding issues.

3. Nonclinical Pharmacology/Toxicology

Based on nonclinical reviews, there are no nonclinical findings that would preclude the approval of axitinib for the proposed indication.

4. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review team recommends approval of this NDA and there are no outstanding clinical pharmacology issues that preclude approval.

5. Clinical Microbiology

There are no outstanding clinical microbiology or sterility issues that preclude approval.

6. Clinical/Statistical-Efficacy

Efficacy of axitinib was demonstrated in an international, randomized, open-label trial in patients with advanced renal cell carcinoma after failure of one prior systemic regimen. The primary efficacy endpoint was PFS.

The trial enrolled 723 patients: 361 patients were assigned to receive axitinib 5 mg orally twice daily, and 362 patients were assigned to receive sorafenib 400 mg orally twice daily. Treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. All enrolled patients had an ECOG performance status of 0 or 1 and all patients had received one prior systemic therapy that contained one of the following treatments: sunitinib, temsirolimus, bevacizumab or cytokine(s). The trial excluded patients who had uncontrolled hypertension.

The PFS analysis demonstrated a statistically significant improvement in PFS in patients receiving axitinib compared to patients receiving sorafenib (HR=0.67; 95% CI: 0.54, 0.81; p< 0.0001, log-rank test). The median PFS of patients receiving axitinib was 6.7 months (95% CI: 6.3, 8.6) compared to a median PFS of 4.7 months (95% CI: 4.6, 5.6) for patients receiving sorafenib. This improvement in PFS was greater in the cytokine-

pretreated subgroup compared to the sunitinib-pretreated subgroup. There was no difference in the final overall survival analysis between the two arms with a hazard ratio of 0.97 (95% CI 0.8-1.17). Please see table below.

Table 1: Table 3. Efficacy Results

Endpoint/Study Population	Axitinib	Sorafenib	HR (95% CI)	P-value
Overall ITT	N= 361	N = 362		
Median PFS[a,b] in months (95% CI)	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)	0.67 (0.54, 0.81)	<0.0001[c]
Median OS in months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	NS
ORR % (95% CI)	19.4 (15.4, 23.9)	9.4 (6.6, 12.9)	2.06[d] (1.41, 3.00)	[e]
PFS by prior treatment				
Sunitinib-refractory subgroup	N=194	N=195		
Median, months (95% CI)	4.8 (4.5, 6.4)	3.4 (2.8, 4.7)	0.74 (0.57, 0.96)	[e]
Cytokine-refractory subgroup	N=126	N=125		
Median, months (95% CI)	12.1 (10.1, 13.9)	6.5 (6.3, 8.3)	0.46 (0.32, 0.68)	[e]

CI: Confidence interval; HR: Hazard ratio (axitinib/sorafenib); ITT: Intent to treat; ORR: Objective response rate; NS: Not significant; OS: Overall survival; PFS: Progression-free survival

[a] Time from randomization to progression or death due to any cause, whichever occurs first.

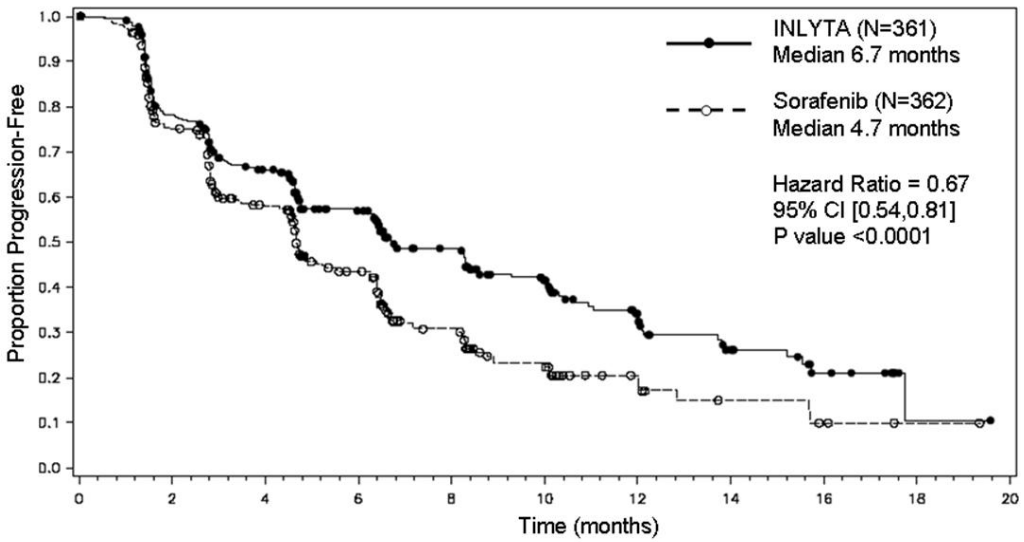
[b] Assessed by independent radiology review according to RECIST.

[c] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy (comparison is considered statistically significant if the one-sided p-value is <0.023).

[d] Risk ratio is used for ORR. A risk ratio >1 indicated a higher likelihood of responding in the axitinib arm; a risk ratio <1 indicated a higher likelihood of responding in the sorafenib arm.

[e] P-value not included since it was not adjusted for multiple testing.

Figure 1: Kaplan-Meier Curve for Progression Free Survival (ITT Population)



7. Safety

The safety of axitinib has been evaluated in 715 patients in monotherapy studies, which included 537 patients with advanced RCC. Per Dr McKee, "The safety profile of axitinib is comparable to that of other drugs in the same class of small molecule inhibitors of the VEGF pathway in terms of the types of adverse events observed.

The most common (≥20%) adverse reactions in patients treated with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation. Other severe adverse reactions reported in axitinib-treated patients included hypertensive crisis, arterial and venous thrombotic events, hemorrhage, gastrointestinal perforation and fistula formation, and reversible posterior leukoencephalopathy syndrome.

The less common, but serious adverse reactions stated above have been included in the Warning and Precautions section. There is no Boxed Warning, REMS, PMRs or clinical PMCs.

8. Advisory Committee Meeting

This NDA was presented to the Oncology Drug Advisory Committee (ODAC). In response to the question "Is the benefit:risk evaluation favorable for axitinib treatment in patients with advanced RCC after failure of a first-line systemic therapy?" All 13 members responded with a unanimous "yes" and there were no abstentions.

It was noted by the ODAC that the toxicity profile of axitinib is different from but manageable compared to other products currently on market and it was generally agreed that axitinib offers an alternative treatment for patients with renal cancer, that it is an active agent that is modestly more effective compared to sorafenib, an approved therapy.

9. Pediatrics

A pediatric waiver was granted because the disease does not exist in children.

10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

11. Labeling

- Proprietary name: The name "INLYTA" was found to be acceptable by DMEPA, OPDP and OHOP.
- Physician labeling; Carton and immediate container labels; Patient labeling/Medication guide: All major issues were discussed and resolved.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.
- Risk Benefit Assessment

A modest improvement in PFS was demonstrated with the use of axitinib compared to sorafenib. Sorafenib is commonly used to treat renal cell cancer; however, its treatment effect as a second-line treatment is not known. The treatment effect of sorafenib should be added to the axitinib PFS benefit to give the total treatment effect of axitinib. In addition, axitinib has a different but generally manageable toxicity profile when compared to other recently approved agents for renal cell cancer. The risk:benefit profile has also been assessed by the Deputy Division Director, CDTL and clinical reviewer, and I concur with their recommendation, as well as other discipline reviewer recommendations to approve this application.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

See action letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAMY E KIM
01/27/2012

RICHARD PAZDUR
01/27/2012