

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202324Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	January 26, 2012
<b>From</b>	Amna Ibrahim MD
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA/BLA #</b>	202324
<b>Supplement #</b>	000
<b>Applicant Name</b>	Pfizer Pharmaceuticals, Inc.
<b>Date of Submission</b>	April 14, 2011
<b>PDUFA Goal Date</b>	February 14, 2012
<b>Proprietary Name / Established (USAN) Name</b>	Inlyta axitinib
<b>Dosage Forms / Strength</b>	Tablet/ 5 mg
<b>Proposed Indication(s)</b>	For the treatment of patients with advanced renal cell carcinoma
<b>Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted OND Action Package, including:</b>	<b>Names of discipline reviewers</b>
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- $\alpha$  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

Kareen Riviere Ph.D. (Biopharmaceutics reviewer/ONDQA) stated that the proposed film coat (b) (4) is acceptable for the 1 mg and 5 mg tablet. This review was cosigned by Sandra Suarez Ph.D. CMC reviewers Amit Mitra Ph.D. and Zhe Tang Ph.D. recommend approval with respect to CMC. Their reviews are co-signed by Sarah Miksinski Ph.D. Richard Lostritto Ph.D. in his Division Director’s memo recommends approval of this NDA. He recommends one CMC-related PMC for this application which provides for the applicant to validate testing for (b) (4) within 90 (ninety) days. Dr Lostritto states that this is a test the applicant ultimately agreed to adopt late in the review cycle and for which they did not have a validated method. Because this is a well known test with a long and well characterized history, ONDQA is comfortable allowing this time to for validation which should be straightforward.

All other CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies from the CMC standpoint.

I concur with the conclusions reached by the chemistry reviewer 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 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**

As stated by Anwar Goheer Ph.D. and Todd Palmby Ph.D. in their reviews, there are no non-clinical findings that would preclude the approval of axitinib for the proposed indication. I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

### **4. Clinical Pharmacology/Biopharmaceutics**

Sarah Schrieber Ph.D., Nitin Mehrotra Ph.D. and Rosane Orbach Ph.D. in their review cosigned by Christine Garnett PhD, Issam Zineh Ph.D., Qi Liu Ph.D. and Nam Atiqur Rahman Ph.D., state that this NDA is considered acceptable from a clinical pharmacology perspective. I concur with the conclusions reached by the clinical pharmacology and biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

### **5. Clinical Microbiology**

Denise A. Miller and Stephen Langille recommend approval from the clinical microbiology perspective. They state that formulated powders are (b) (4) film coated and packaged. This is a non-sterile drug product. I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

### **6. Clinical/Statistical-Efficacy**

Efficacy of axitinib is based on a single randomized, open-label, multicenter Phase 3 trial comparing axitinib to sorafenib as second-line systemic therapy in patients with metastatic renal cell carcinoma. Patients were randomized to receive either axitinib 5 mg po BID or sorafenib 400 mg po BID. The primary efficacy endpoint was PFS as assessed by a blinded Independent Review Committee. Secondary endpoints included overall survival and objective response rate (ORR), and safety of axitinib. This protocol was granted an SPA.

A total of 723 patients were randomized to receive axitinib or sorafenib. Of the patients enrolled in this study, 389 patients (54%) had received 1 prior sunitinib-based therapy, 251 patients (35%) had received 1 prior cytokine-based therapy (interleukin-2 or IFN- $\alpha$ ), 59 patients (8%) had received 1 prior bevacizumab-based therapy, and 24 patients (3%) had received 1 prior temsirolimus-based therapy. The baseline demographic and disease characteristics were similar between the axitinib and sorafenib groups

A statistically significant improvement in PFS was demonstrated 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 on the sorafenib arm. This improvement in PFS was greater in the cytokine-treated subgroup compared to the sunitinib-refractory 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**

(from Package Insert)

Endpoint/Study Population	Axitinib	Sorafenib	HR (95% CI)	P-value
<b>Overall ITT</b>	N= 361	N = 362		
Median PFS <sup>a,b</sup> in months (95% CI)	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)	0.67 (0.54, 0.81)	<0.0001 <sup>c</sup>
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 <sup>d</sup> (1.41, 3.00)	<sup>e</sup>
<b>PFS by prior treatment</b>				
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)	<sup>e</sup>
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)	<sup>e</sup>

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

<sup>a</sup> Time from randomization to progression or death due to any cause, whichever occurs first.

<sup>b</sup> Assessed by independent radiology review according to RECIST.

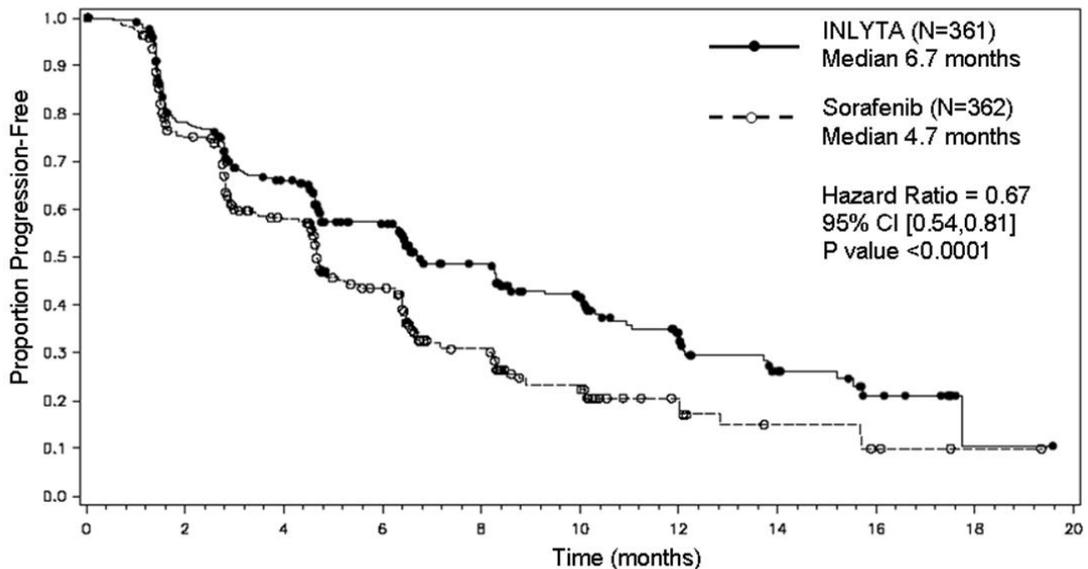
<sup>c</sup> One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy (comparison is considered statistically significant if the one-sided p-value is <0.023).

<sup>d</sup> 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.

<sup>e</sup> P-value not included since it was not adjusted for multiple testing.

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

(from Package Insert)



## 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. Common adverse events include diarrhea, nausea, fatigue, asthenia, hypertension, dysphonia and dermatologic adverse events. Less common serious adverse events include arterial and venous thrombotic events, gastrointestinal perforation, bleeding events, hypothyroidism, proteinuria and reversible posterior leukoencephalopathy syndrome. There were no new signals for serious adverse events with axitinib that had not been previously identified for this class of drugs.”

Per John Johnson M.D. (CDTL), “the frequency and severity of adverse reactions was similar for axitinib and sorafenib. However, the adverse reaction profile was different. Hypertension, dysphonia, and hypothyroidism are more frequent for axitinib than sorafenib. Hand-foot syndrome, rash, and alopecia are more frequent for sorafenib than axitinib.”

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

Because axitinib is an NME, this NDA was presented to 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

- DSI Audits: Four sites (2 in Europe and 2 in US) were inspected. One foreign site had a “major objectionable finding related to the documentation of updated consent and not to data integrity.” Per MO Dr McKee, she did not believe it affected the findings of the Phase 3 trial. Neither is there evidence of widespread issues with Good Clinical Practices. It is stated in the DSI review by Robert Young MD that there were no

significant regulatory findings relating to data integrity from any of the four sites inspected. The data may be used in the evaluation of this application.

- Financial Disclosure: Per Dr Johnson, and Dr McKee, investigators who conducted the clinical trials supporting this NDA and who had no financial interests to disclose were submitted in the FDA form 3454. The disclosure was certified by D. Stuart Sowder, Vice President-External Medical Communication for the applicant. Disclosure of financial interests of the investigators who conducted the clinical trials supporting this NDA was submitted in the FDA form 3455. Thirty-three investigators in the key study supporting this NDA were found to have financial conflict of interest, either a proprietary interest or significant payments from or equity interest in the applicant. These investigators received payments as honoraria for speaking events, professional fees and consulting fees ranging from totals of \$27,325 to \$510,650. These investigators enrolled a total of 81 patients onto the Phase 3 trial, ranging from one to 15 patients at each site. While this represents slightly over 10% of the total patient population in the Phase 3 trial, it is unlikely that any single investigator could have influenced the efficacy results of the trial.

It is also noted that the primary endpoint of PFS was based on a blinded, independent review that would not be expected to be influenced by financial conflicts of these investigators.

- Other consults- All consultants comments were incorporated during labeling meetings.

There are no other unresolved relevant regulatory issues

## **11. Labeling**

Includes:

- Proprietary name: The name “INLYTA” was ultimately chosen as the proprietary name.
- Physician labeling: All major issues were discussed and resolved. The indication was modified to reflect the patient population studied.
- Carton and immediate container labels: All major issues were discussed and resolved.
- Patient labeling/Medication guide: All major issues were discussed and resolved.

## **12. Decision/Action/Risk Benefit Assessment**

- Regulatory Action

I agree with the Medical Officer’s and CDTL’s recommendation as well as those from other disciplines as noted earlier. I recommend approval for the following indication:

*“INLYTA is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.”*

- 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. This approval will provide an option for the treatment of patients with renal cell cancer who have received one prior systemic therapy.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No REMS are proposed by DRISK or the primary team and none are required.

- Recommendation for other Postmarketing Requirements and Commitments

One CMC-related PMC will be included in the action letter. This PMC is as follows:

“Provide the analytical methods and method validation for testing of (b) (4) and (b) (4) in the final drug substance”

The final report submission date agreed to by the sponsor is April 22, 2012. Dr Lostritto stated in his ONDQA Division Director’s memo that this is a test the applicant agreed to adopt late in the review cycle and for which they did not have a validated method. Because this is a well known test with a long and well characterized history, ONDQA is comfortable allowing this time to for validation which should be straightforward.

Amna Ibrahim M.D.,  
Deputy Director,  
Division of Oncology Products 1

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/s/  
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AMNA IBRAHIM  
01/26/2012