Labeling Supplement – Clinical Review

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Review Completion Date	See Electronic Stamp Date
Division/Office	CDER/OOD/DO1
Medical Officer	Mahta Mahmoudieh
Team Leader	Sundeep Agrawal
Signatory	Christy Osgood
Product: Established Name (Trade name)	Axitinib (INLYTA)
Formulation	Tablets, for oral use
Established Pharmacologic Class (EPC)	Kinase inhibitor
Applicant	Pfizer Inc.
Recommended Regulatory Action	Approval

1. Executive Summary:

This supplemental New Drug Application (sNDA) was submitted to complete the Applicant's response to the Pediatric Written Request (PWR) Amendment 3 and to request additional marketing exclusivity: Pediatric Exclusivity, based on the pediatric information as provided under Section 505A of the Federal Food, Drug, and Cosmetic Act. The Applicant proposed labeling revisions to Section 8.4, "Pediatric Use," of the U.S. Prescribing Information (USPI) to include the results of pediatric studies conducted with axitinib without pursuing an indication in the pediatric population, as the available data do not conclusively support a favorable benefit/risk profile for axitinib in the treatment of pediatric patients. The Applicant met the terms of the PWR Amendment 3 and revisions to the USPI are justified as the available information from the pediatric studies, even with smaller sample sizes precluding formal hypothesis testing in Study 2, provide descriptive information to inform labeling for axitinib in the treatment of pediatric patients. The revisions made in this supplement include adding the following language to Section 8.4, Pediatric Use:

> *The safety and effectiveness of INLYTA were assessed, but not established, in two open label studies: a dose finding study of INLYTA as a single agent in 17 pediatric patients aged 5 to <17 years with recurrent or refractory solid tumors (ADVL1315, NCT02164838) and a randomized study of INLYTA as a single agent or in combination in 7 pediatric patients aged 7 to <17 years (AREN1721, NCT03595124).*
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> *No new safety signals were observed with INLYTA in pediatric patients across these studies. Exposure in pediatric patients who received INLYTA at the maximum tolerated dosage were lower than those previously observed in adults who received the approved recommended starting dosage.*

2. Regulatory Background

Axitinib is a tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR), indicated, 1) In combination with avelumab for the first-line treatment of patients with advanced renal cell carcinoma, 2) In combination with pembrolizumab for the first-line treatment of patients with advanced renal cell carcinoma, and 3) As a single agent for the treatment of advanced renal cell carcinoma after failure of one prior systemic treatment. Axitinib was initially approved for marketing in the United States on January 27, 2012. In the Applicant's approval letter, the FDA waived the pediatric study requirement for the application because studies were considered impossible or highly impracticable in pediatric patients with advanced renal cell carcinoma. In accordance with the FDA's Guidance for Industry entitled, "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act" and the Best Pharmaceuticals for Children Act, on June 3, 2019, the Applicant submitted a Proposed Pediatric Study Request (PPSR) for axitinib and requested the issuance of a Written Request (WR) for the evaluation of axitinib in advanced translocation renal cell carcinoma (tRCC) to support the use of axitinib in the pediatric population.

On August 6, 2019, the FDA issued an Inadequate Study Request letter stating that the Sponsor should justify why tRCC is the only indication being evaluated, asking for specification of the minimum number of pediatric patients to be enrolled in studies, and requested PK data and exploration of exposure-response relationships between axitinib systemic exposure and selected efficacy and toxicity endpoints. Between August 2019 and August 2020, the Sponsor and FDA had multiple correspondence regarding the PPSR and FDA finally issued the WR for axitinib on August 3, 2020. The WR was amended on April 18, 2022 (Amendment #1) and on August 30, 2023 (Amendment #2) and again on January 3, 2024 (Amendment #3). The WR was amended on April 18, 2022, (Amendment #1) to align with COG/NCI protocol changes to optimize feasibility of Study 2 due to slow accrual. On August 30, 2023, the Written Request was amended (Amendment #2) to incorporate additional changes to Study 2 due to persistent accrual difficulties despite due diligence to facilitate timely enrollment and subsequent closure of Study 2. Amendment #2 reduced the minimum number of patients required and changed the statistical analysis plan to be descriptive in nature. Amendment #3 updated the required information for reporting information on the representation of pediatric patients of ethnic and racial minorities.

3. Background and Review of Clinical Data

The WR consists of three studies that investigate the potential use of axitinib in the treatment of pediatric patients with recurrent or refractory solid tumors, including advanced translocation renal cell carcinoma.

- Study 1: ADVL1315 (n=19), "A Phase 1 study of the VEGF receptor tyrosine kinase inhibitor axitinib in children with recurrent or refractory solid tumors"
- Study 2: AREN1721, "A randomized Phase 2 trial of axitinib/nivolumab combination therapy vs. single agent nivolumab for the treatment of transcription factor E3 (TFE)/translocation renal cell carcinoma (tRCC) across all age groups"
- Study 3: Pooled pharmacokinetic (PK) Analysis: The objectives of population PK (popPK) analysis in pediatric patients are to explore the effect of age and body size on axitinib CL/F and V d/F and make predictions on the dosing of axitinib in pediatric patients in different age groups.

The Applicant planned to incorporate the adult PK data from the adult popPK model (PMAR-00079) into the pediatric popPK analysis. The Applicant stated that given the limited number of pediatric patients with translocation renal cell carcinoma (tRCC) in Study AREN1721 and the heterogeneity in patients' tumor types in Study ADVL1315 and Study AREN1721, an exposure-response (E-R) analysis for efficacy is not expected to yield meaningful results. Therefore, the Applicant proposed to only conduct E-R safety analyses with respect to key safety endpoints, rather than key safety and efficacy endpoints.

The Applicant initially proposed a labeling revision to incorporate the safety results from study 1: ADVL1315, Study 2: AREN1721, and population pharmacokinetic analyses from Study 3. No new indications or changes to existing indication statements were proposed for this labeling update.

Study 1: ADVL1315

Study Design

ADVL1315 was a Phase 1 trial to estimate the maximally tolerated dose (MTD) or recommended phase 2 dose (RP2D), describe the toxicities, and characterize the pharmacokinetics of axitinib administered orally twice daily in pediatric patients with refractory solid tumors. Secondary aims were to describe the antitumor activity of axitinib within the confines of a phase 1 study, and to investigate biomarkers of acute kidney injury (AKI) and nephrotoxicity. Patients aged >12 months and <18 years of age were enrolled with a minimum of 3 evaluable patients at each dose level for determination of MTD and up to 6 additional patients were allowed to enroll after determination of MTD or RP2D to acquire PK data. 19 patients were enrolled with 13 patients assigned to Dose Level 1 (Starting dose level; 2.4 mg/m^2 BID) and 6 patients to Dose Level 2 (3.2 mg/m^2 BID). 2.4 mg/m2 (~80% of the adult-recommended starting dose) was determined as the MTD/RP2D of axitinib, administered orally BID.

Safety Findings

DLTs were observed at Cycle 1, Dose Level 2 only. Two (2) patients (33.3%) reported TEAEs considered to be DLTs: 1 patient reported a Grade 3 tumor hemorrhage and 1 patient reported Grade 2 palmar-plantar erythrodysesthesia. The patient with Grade 3 tumor hemorrhage permanently discontinued study treatment due to the DLT. All patients reported at least 1 TEAE and treatment-related TEAE. The most common (>50%) all causality TEAEs in all patients were hypertension, nausea, anemia, headache, and pain in extremity; the most common (>45%) treatment related TEAEs in all patients were diarrhea, hypertension, and nausea. Clinically significant liver function abnormalities were reported as TEAEs; these were all Grade ≤2 except for 1 patient who experienced 1 Grade 3 AST, but no potential Hy's Law cases were reported. Two (2) patients (15.4%) from Dose Level 1 died within 30 days of the last dose of axitinib, but both deaths were assessed by the investigator as not related to study treatment and were related to the disease under study. All-causality SAEs were reported for 8 patients (42.1%); 6 patients (46.2%) at Dose Level 1 and 2 patients (33.3%) at Dose Level 2. SAEs reported by >1 patient were pleural effusion, hypoxia, and respiratory failure. Treatment related SAEs occurred in 5 patients (26.3%).

Efficacy Findings

Confirmed objective response rate (ORR) based on RECIST v1.1 and duration of response (DR) were determined. Of the 19 participants enrolled, 1 (5.3%) patient with alveolar soft tissue sarcoma had a best overall response of PR with a duration of 9.5 months, 5 (26.3%) patients had SD during treatment,

with a duration of 2.7 to 5.6 months, and 11 (57.9%) patient had PD. CR was not observed for any of the 19 participants.

Study 2: AREN1721

Study Design

AREN1721 was a randomized Phase 2 trial of axitinib/nivolumab combination therapy vs. single agent nivolumab for the treatment of TFE/translocation renal cell carcinoma (tRCC) across all age groups. The primary objectives were to establish the clinical activity, assessed primarily by PFS, of nivolumab therapy with or without axitinib for advanced transcription factor E3/translocation morphology renal cell carcinoma (TFE/tRCC). The secondary objectives were to establish the clinical activity through assessment of ORR and OS and to characterize the safety and tolerability of nivolumab, with or without axitinib and to explore the PK of axitinib when given in combination with nivolumab in the pediatric population. A minimum of 12 patients ≥12 months of age at enrollment, with unresectable or metastatic tRCC were planned for enrollment. Randomization planned to incorporate stratification (<18 years vs. ≥18 years) and prior systemic therapy for RCC (none, anti-VEGF therapy, systemic therapy other than anti-VEGF). The study was required by the PWR Amendment 3 to enroll at least 2 patients aged 12-17 years (inclusive) and 3 patients younger than 12 years in the axitinib/nivolumab combination arm. A total of 12 patients were randomly assigned to one of the 2 treatment arms (axitinib +nivolumab, N=7 or nivolumab alone, N=5). Two patients aged 12-17 years (inclusive) and 3 patients less than 12 years of age were enrolled in the axitinib + nivolumab combination arm. One patient crossed over from nivolumab monotherapy arm to the combination arm. The primary endpoint was progression free survival (PFS).

Safety Findings

All causality TEAEs were experienced by 71.4% (5/7), 60.0% (3/5), and 100.0 % (1/1) of participants in Arm A, Arm C, and the Crossover arm, respectively. No Grade 4 or Grade 5 TEAEs were reported. In Arm A, the TEAEs of blood creatinine increased, headache, hypertension, oral pain, and proteinuria were reported for 2 participants each, all other TEAEs were reported for 1 participant each. Of these, the TEAEs in Arm A that were Grade 3 in intensity included: anemia, eosinophilia, headache, noncardiac chest pain, oral pain, proteinuria, pericardial effusion, pleural effusion, hypertension, and pneumothorax and were reported for 1 participant each. In Arm C, the TEAEs of decreased appetite, nausea, pneumothorax, dehydration, lymphocyte count decreased, portal vein thrombosis, and vomiting were reported for 1 participant each and all were Grade 3 in intensity. In the Crossover Arm, the Grade 3 TR TEAE of pneumonia was reported for 1 participant.

Efficacy Findings

A PFS event was reported for 83.3% (5/6) and 75.0% (3/4) of patients in Arm A and Arm C, respectively. Median PFS was 7.2 months (70% CI: 5.7, 11.6) for patients in Arm A and 1.8 months (70% CI: 0.8, NE) for patients in Arm C. Complete response was not reported for any patient in any treatment arm. In Arm A, PR was reported for 3 participants, however, target lesion assessments for 1 participant do not support the finding of PR as best overall response. This incorrect assessment invalidated the reported 95% CI values for Arm A. DOR for the 2 participants with PR in Arm A was 3.8 and 3.2 months. In Arm A, the best overall response of PR was reported for 2 pediatric participants and SD responses were reported for 2 pediatric participants and 1 adult participant. OS events were reported for 14.3% (1/7)

and 60.0% (3/5) of participants in Arm A and Arm C, respectively. Median OS for participants Arm A was NE (70% CI: 28.6, NE) and 21.8 months (70% CI: 15.4, NE) for participants in Arm C. Median duration of follow-up for OS using the reverse Kaplan-Meier method was 14.8 months and 23.8 months for participants in Arm A and Arm C, respectively. The unstratified HR for OS (Arm A vs Arm C) was 0.01; 70% CI: 0.001, NE; 2-sided p=0.0629). One patient crossed over from Arm C to Arm A.

Study 3

Study 3 was a pooled pharmacokinetic (PK) Analysis of studies 1 and 2 planned to explore the effect of age and body size on axitinib CL/F and Vd/F and make predictions on the dosing of axitinib in pediatric patients in different age groups. In total, 226 PK observations from 22 pediatric participants were available for the PK dataset. Due to the limited pediatric axitinib PK data available, the popPK model integrated adult axitinib PK data from the final adult popPK model presented in the original NDA submission. The final popPK model demonstrated pediatric participants with larger body size (body surface area [BSA]) typically had larger central volumes of distribution (Vc). The inclusion of BSA on Vc, while significant as determined by the popPK model, did not explain the high axitinib PK variability. After incorporating the effect of BSA on Vc, age was not a significant covariate on CL or Vc. Overall, neither body size nor age were considered to have clinically meaningful impacts on axitinib PK in the pediatric population. This was consistent with the adult popPK analysis, where body weight had a significant influence on axitinib Vc but did not substantially decrease the high variability associated with axitinib disposition.

Reviewer Comments: During the time period between issuance of the Written Request and the subsequent amendments, the Applicant provided information demonstrating multiple efforts to promote accrual throughout the conduct of Study 2, and that accrual lagged severely despite these substantive efforts. During this period, treatment with a checkpoint inhibitor and VEGF agent became the de facto standard of care for pediatric patients with tRCC due to emerging data regarding the higher level of activity of the combination compared to single agent checkpoint inhibitor chemotherapy alone.

Although the smaller sample size of Study 2: AREN1721 precludes it from formal hypothesis testing, it provided descriptive information to inform labeling for axitinib in the treatment of pediatric patients. It is important to consider these data in the context of an extremely rare disease, for which treatment patterns evolved rapidly between the time of issuance of the Written Request and the time of the subsequent amendments.

4. Labeling changes

Table 1 summarizes revisions proposed by the Applicant for all sections of the Prescribing Information containing or referencing clinical data and relevant justification and recommendation from the FDA clinical review team. New text is underlined and deleted text is ~~struck through~~.

Table 1. Proposed Revisions to US Prescribing Information

(b) (4)

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5. Recommended Regulatory Action

Overall, the FDA review team found the Applicant to have met the terms of the PWR Amendment 3 and recommends approval of the Pediatric Exclusivity request as summarized in this review. Additionally, the pediatric information has been updated in Section 8.4 of labeling.

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/s/

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