NDA/Supplement (SDN)	125477/S39 (1180) Link
Submission Type	Labeling supplement
Applicant Name	Eli Lilly
Submission Date	12/18/2020
Generic Name	Ramucirumab (Cyramza®)
Dosage Form (Strength)	100 mg/10 mL (10 mg/mL) or 500 mg/50 mL (10 mg/mL) solution in a single-dose vial
Indication	Pediatric solid tumors
Clinical Pharmacology Reviewer	Amal Ayyoub, PhD
Team Leader	Hong Zhao, PhD

1 Executive summary

In the current labeling supplement, Eli Lilly submits the final study report and datasets of a Phase 1 trial, JVDA, titled "*A Phase 1 Study of Ramucirumab, A Human Monoclonal Antibody Against the Vascular Endothelial Growth Factor-2 (VEGFR-2) Receptor in Children with Refractory Solid Tumors, Including CNS Tumors*".

Section 8.4 of the Cyramza® label has been updated to report the lack of efficacy in this population and that pharmacokinetic (PK) parameters in pediatric patients were within range of the values previously observed in adults. The Office of Clinical Pharmacology has reviewed the submission and concluded that the results of Study JVDA support the proposed labeling changes provided that the Applicant and FDA reach agreements on label languages.

2 Background

Cyramza® is a recombinant human IgG1 monoclonal antibody that is a vascular endothelial growth factor receptor 2 (VEGFR2) antagonist. Cyramza® (BLA 125477) is approved for the treatment of adult patients with advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma, metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations, or hepatocellular carcinoma. The recommended dosage for adults is 8 mg/kg every 2 weeks (Q2W; gastric cancer), 10 mg/kg Q2W (non-small cell lung cancer), or 8 mg/kg Q2W (hepatocellular carcinoma).

In the current submission, Eli Lilly submits the final study report and datasets of a Phase 1 trial, JVDA, titled "*A Phase 1 Study of Ramucirumab, A Human Monoclonal Antibody Against the Vascular Endothelial Growth Factor-2 (VEGFR-2) Receptor in Children with Refractory Solid Tumors, Including CNS Tumors*", and updates the Cyramza USPI.

3 Clinical Pharmacology Evaluation

In the current submission, Eli Lilly submits the final study results from Study JVDA; a multicenter, open-label, dose-finding study of ramucirumab monotherapy in children aged ≥12 months and patients ≤21 years of age with recurrent solid tumors. The primary objective was to estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ramucirumab administered as an IV infusion over 60 minutes, Q2W, to children with recurrent or refractory solid tumors. The PK endpoint was to determine if $C_{min,ss}$ ≥50 µg/mL is achieved per a 42-day treatment course. The study consisted of 2 parts;

- Part A (n=24) was a PK, dose finding, safety, and preliminary efficacy study in patients with recurrent or refractory non-CNS solid tumors using a rolling-6 design. Two dosing regimens were evaluated; 8 mg/kg Q2W (n=8), and 12 mg/kg Q2W (n=15). A third dosing regimen (≤16 mg/kg Q2W) was to be considered only after evaluation of PK and toxicity at 12 mg/kg Q2W.
- Part B (n=6) included additional safety and imaging evaluation in patients with recurrent or refractory CNS solid tumors at the RP2D determined in Part A. The dosing regimen evaluated is 12 mg/kg Q2W.

In Part A, two patients, one at each dose level in Part A experienced a dose limiting toxicity (DLT) of Grade 2 proteinuria. The MTD was not reached as only 1 patient in each dose level experienced a DLT. The Day 43 $C_{min,ss}$ data was analyzed for 4 DLT-evaluable patients at Dose Level 1, of which 2 patients had a Day 43 $C_{min,ss}$ result <50 μg/mL. The criteria for RP2D based on trough concentration was not met at Dose Level 1. At Dose Level 2, of the 12 DLT-evaluable patients who had Day 43 $C_{min,ss}$ data reported during the observation period, 10 patients had Day 43 $C_{min,ss}$ results that exceeded the 50 μg/mL target. Therefore, the RP2D of ramucirumab was declared to be 12 mg/kg IV Q2W for pediatric and young adult patients (≥12 months to ≤21 years). A total of 21 patients (15 in Part A with non-CNS tumors and 6 in Part B with CNS tumors) were treated at the determined RP2D of 12 mg/kg Q2W.

Overall, the observed safety profile of the patients treated at this dose level was generally consistent with the studies of single agent ramucirumab in adult advanced cancer patients. All 21 patients in the safety population who were administered ramucirumab at 12 mg/kg Q2W, experienced at least 1 any grade treatment emergent adverse event (TEAE), of which 11 patients (52.4%) had Grade ≥3 TEAEs. One patient in Part A had a Grade 4 TEAE of hypocalcemia. Grade 3 TEAEs observed in 2 or more patients were: dyspnea, lymphocyte count decreased and, pyrexia (2 patients, 9.5% each). Twenty patients (95.2%) experienced at least 1 any-grade TEAE assessed as related to study treatment, of which 4 patients (19%) experienced Grade 3 TEAEs; none of which were reported in more than 1 patient. No Grade 4 or 5 TEAEs were observed. One patient in Part A at Dose Level 2 discontinued from study treatment due to DLT of Grade 2 proteinuria.

Of the 29 patients treated, 11 (37.9%) had closed growth plates and 18 (62.1%) had open growth plates at baseline. Of the 18 patients with an open growth plate, 13 patients had a follow-up growth plate radiograph prior to starting Cycle 2. Of these 13 patients, 1 patient in Part B had a progressive widening of the distal femoral growth plate that was apparent in 2 successive follow-up radiographs. Since no subsequent off-treatment growth plate radiographs were obtained, long-term outcome remains unknown.

Ramucirumab C_{max} and AUC increased in a dose proportional fashion (1.5-fold) from 8 mg/kg to 12 mg/kg. T_{max} occurred approximately 1-hour post start of infusion. Ramucirumab clearance (range 2.5 to 28 mL/hr) increased with body weight (range 8.7 to 91 kg), and decreased with time following multiple doses, as expected based on adult patient data. Ramucirumab volume of distribution was similar to the blood volume and the mean half-life was approximately 10 days (ranging from 5 to 21 days following multiple doses). Ramucirumab exposure following 12 mg/kg Q2W dose is similar across the age range (≥12 months to ≤21 years) of the pediatric patients enrolled at this dose supporting that the weight-based dosing is appropriate. Ramucirumab PK data in pediatric patients from Study JVDA were compared to the simulated PK profile based upon the population PK model developed using the large ramucirumab PK database in adult patients. Ramucirumab exposure in pediatric patients was similar to ramucirumab exposure reached in adult patients at the corresponding 12 mg/kg dose (Tables 1 and 2).

Table 1. Comparison of Ramucirumab Trough (C_{min}) Concentrations between Pediatric Patients in Study JVDA and Adult Studies Following Ramucirumab 12 mg/kg Q2W Administration

C_{trough} (predose Day 43)	N	Geometric Mean (µg/mL)	CV%
Pediatric patients ≥ 12 months to ≤ 21 years	14	80.2	44
Pediatric patients ≥ 12 months to < 17 years	10*	72.9	48.1
Adult patients (Study JVCZ)	84	76.7	42
Adult patients (Study JVDB)	22	71.0	58

Source: Prepared by the reviewer.
* Number of pediatric patients ≥ 12 months to < 17 years of age with available C_{trough} concentrations.

Table 2. Comparison of Ramucirumab Peak Concentrations between Pediatric Patient in Study JVDA and Adult Studies following Ramucirumab at 12 mg/kg Q2W Administration

C_{max} (Day 29, 1-hour post-end of infusion)	N	Geometric Mean (µg/mL)	CV%
Pediatric patients ≥ 12 months to ≤ 21 years	19	345	27
Pediatric patients ≥ 12 months to < 17 years	14*	302.3	34
Adult patients (Study JVCZ)	84	292	25
Adult patients (Study JVDB)	22	303	23

Source: Prepared by the reviewer.
* Number of pediatric patients ≥ 12 months to < 17 years of age with available C_{max} concentrations.

Immunogenicity samples were analyzed for 28 of the 29 patients treated with ramucirumab for the presence of anti-ramucirumab antibodies. None of the 28 evaluable patients had ADAs detected at baseline. All 28 patients tested negative for postbaseline treatment emergent ADAs.

(b) (4)

4 Labeling

The following labeling language with double underlines represents added language included in Section 8.4 "Pediatric Use" in the Applicant's proposal:

The safety and pharmacokinetics (PK) of CYRAMZA, as a single agent, were (b) (4) in a multicenter, open-label, (b) (4) study (b) (4)

FDA recommends the following labeling language be included in Section 8.4 to describe the safety and effectiveness in pediatric patients and similar PK results in pediatric patients compared to adult patients:

The safety and effectiveness of CYRAMZA in pediatric patients have not been established.

The safety and effectiveness of CYRAMZA as a single agent were assessed but not established in a single-arm, multicenter, open-label study [NCT02564198] that included 23 pediatric patients aged 1 year to 16 years with relapsed or refractory solid tumors. The effect on open tibial growth plates in pediatric patients who received CYRAMZA has not been adequately studied; however, one patient in this study had progressive widening of distal femoral growth plate. No other new safety signals were observed in pediatric patients. The pharmacokinetics (PK) for these pediatric patients was within the range of the values previously observed in adults given the same dose per body weight.

5 Conclusions

The results of Study JVDA are incorporated in the USPI of Cyramza.

6 Signatures

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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